A.M.A.
American Journal of DISEASES OF CHILDREN

NOVEMBER 1955
VOLUME 90 NUMBER 5

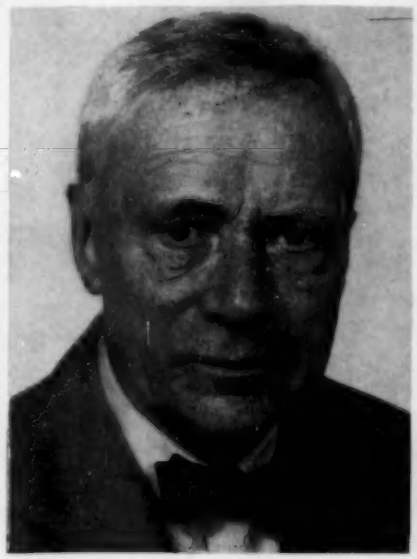
PRESENTATION OF THE JOHN HOWLAND MEDAL AND AWARD OF THE AMERICAN PEDIATRIC SOCIETY TO DR. JAMES L. GAMBLE

INTRODUCTION AND PRESENTATION BY DR. ALLAN M. BUTLER

ACCEPTANCE BY DR. JAMES L. GAMBLE

AMERICAN PEDIATRIC SOCIETY, BRITISH PAEDIATRIC ASSOCIATION, THE SOCIETY FOR PEDIATRIC RESEARCH, AND THE CANADIAN PAEDIATRIC SOCIETY—SOCIÉTÉ CANADIENNE DE PÉDIATRIE

Dr. James L. Gamble



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American Journal of Diseases of Children

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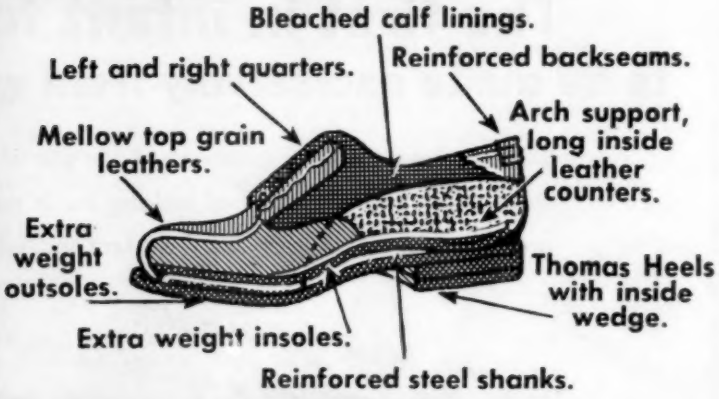

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1. Gyorgy, P.: On Some Aspects of Protein Nutrition, Am. J. Clin. Nutrition 2:231 (July-Aug.) 1954.
2. Davies, J.N.P.: Kwashiorkor. Trans. Ninth Conf. on Liver Injury, Josiah Macy, Jr. Foundation, 1950, p. 109.
3. The National Food Situation, Washington, D. C., Agricultural Marketing Service, United States Department of Agriculture, Oct. 29, 1954. p. 4.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.

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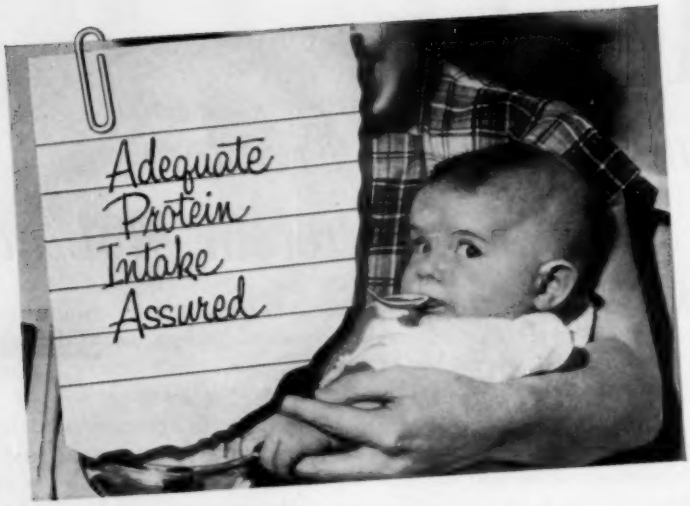

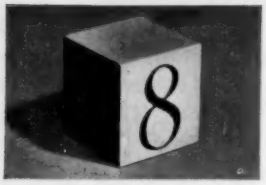

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PRESENTATION OF THE JOHN HOWLAND MEDAL AND AWARD OF THE AMERICAN PEDIATRIC SOCIETY TO DR. JAMES L. GAMBLE

At the Sixty-Fifth Annual Meeting, June 15, 1955, Quebec, Canada

INTRODUCTION AND PRESENTATION BY DR. ALLAN M. BUTLER

PRESENTATION on behalf of the American Pediatric Society of the John Howland Award for 1955 to a teacher whose lectures in the second year of medical school were so inspiring as to determine the direction of one's professional life and to a colleague and friend who over a period of 30 years generously extended the privilege of collaborating in his clinical investigations and enriched one's life in innumerable ways is a gratifying privilege. It is, however, a disturbing assignment, for among the many of you to whom James Lauder Gamble means so much are those who could express the Society's tribute far better. Their knowledge of Dr. Gamble would extend back some 10 years earlier, and their wisdom would suggest how to avoid both repetition and plagiarism from published tributes and biography familiar to most of you.

To circumvent the former, biographical details will be left to the written record, while to avoid the latter I shall quote freely therefrom.

In a warm tribute and delightful description of Dr. Gamble's early years on the occasion of the presentation of the Kober Medal by the Association of American Physicians in 1951 [1] (an award given to only one other member of the American Pediatric Society, namely, Dr. Edwards A. Park) Dr. Robert Loeb commented:

> He has always exhibited a propensity for quiet contemplation and early developed the capacity to design simple experiments which yielded definitive answers . . . each of his works reflects clarity of expression, a rare sense of proportion, a capacity for self-criticism and discipline and, with all, a disarming modesty.

In referring to the classical study of fasting undertaken in 1919, Dr. Loeb continues:

> At a time when most clinical investigation consisted of the recording of endless observations based on some new method, Gamble planned a crucial experiment to elucidate basic problems of function and applied chemical methods to this end. . . . Meaning received the primary emphasis. It was thrilling for those of us who were in Baltimore to see something happening to figures other than tabulation, to see them come to life and illuminate the processes of the acid-base equilibrium. The general design of the experiments devised by Gamble continues to be the pattern for most studies dealing with electrolyte and water metabolism today. Even the expression of data by simple graphic means, now known as Gambelian diagrams or Gamblegrams, has been generally adopted and is a blessing for students, teachers and investigators alike.

Worthy of note as indicative of the thought that has made each of Dr. Gamble's publications so meaningful is the fact that this paper on the metabolism of "Fixed Base During Fasting" was not published until 1923, a year after his moving to Boston.

In accepting the Kober Medal Dr. Gamble with characteristic humility attributed his accomplishments to "a long series of gifts of chance." He expressed his indebtedness during his years at the Massachusetts General Hospital—as an intern 1910-1912 and as a research fellow in 1914—to Drs. Joseph Pratt, Frederick Shattuck, Otto Folin, Wal-

ter W. Palmer, Henry Newburgh, and Lawrence Henderson, commenting,[3]

> Although I never worked directly with Henderson, I learned from him to admire the beauty of the physio-chemical systems which sustain the body fluids, the marvel of their automaticity and their remarkable resiliency in the presence of obstacles imposed by disease, and ever since I have been content to work in this wide field as an humble artisan applying the simple tool of quantitative description to the pattern provided by this great architect of concept.

While this interest was gathering momentum, Dr. Gamble's first paper with Dr. J. H. Means and W. W. Palmer, on "Basal Metabolism and Creatinine Elimination," indicated the nicety of experimental design, conciseness of presentation, and scientific significance that was to characterize all his studies. Mention also should be made of the study with Dr. Kenneth Blackfan in 1920 on the relation of preformed cholesterol in food to total cholesterol metabolism in infants by comparing cholesterol intake and output. The results indicated a synthesis of cholesterol within the organism that should have dampened the ardor of the recent advocates of low-cholesterol diets and have obviated the need of expending several hundred thousand dollars to confirm Dr. Gamble's finding of 30 years ago.

"Gifts of Chance" also came to him in Baltimore, when, as he comments:

> The unusual opportunity to describe water and electrolyte balances and the processes of neutrality regulation under the stationary and simplified circumstances produced by absence of food intake was provided by a reported observation that the seizures of epilepsy disappear during fasting. Here the machination of fortune which gave us permission to fast children was a bit devious. The observation of the effect of fasting on epileptics had been made by a physical culturist who was not a physician. Obviously, however, it would be ungracious and absurd to ask for orthodoxy in the processes of chance. Indeed, I find in my Bartlett the statement that:
>
> "Dame Fortune is a fickle gipsey
> And always blind and sometimes tipsey."
>
> Perhaps you will say that is why we have been so companionable.
>
> Those of us who were early members of Dr. Howland's group were given such a long lead over our contemporaries that important posts in pediatrics over the country eventually came to us quite automatically. We were enthusiastically aware of our *avant garde* position and we had a splendid time together.

As well might a group composed of men such as Drs. Howland, Edwards A. Park, McKim Marriott, Grover Powers, Kenneth Blackfan, Benjamin Kramer, Fred Tisdall, Graham Ross, and James L. Gamble, even though there had been no interludes of golf at Pine Valley between the preparation of papers and their presentation before the Young Turks at Atlantic City each spring. These trips were made in Dr. Gamble's French grey 1915 Cadillac touring car that was loaded on the return trip through Philadelphia with such laboratory equipment as could be purchased with the yearly unexpended balance that otherwise would be returned on June 30 to the University. The Cadillac was the same that some of you will remember in Sorrento as late as 1928. It had by design, not accident, no door to the front seat, to which Dr. Gamble would graciously assist a lady while politely warning her of the hazards incident to absence of floor boards.

Fortunately, these Pine Valley interludes continued after Dr. Gamble joined Dr. Oscar Schloss in Boston in 1922, New Haven's Quaker providing comparatively conventional transporation to Philadelphia. Here on being joined by such men as Thomas Addis and Harold Faber, a very different Cadillac would whisk the group to breakfast at the club, where 27 holes of golf and the subsequent physical and spiritual relaxation on the terrace overlooking the lake bordered by spring blossoms and populated by wild ducks and swans stimulated such philosphical discussion as to justify delaying arrival at the medical meetings by one or more days, depending on the weather, the golf scores, and the philosophical inspiration.

When, Dr. Gamble continues:

> To my consternation Dr. Schloss returned to New York within a year and I found myself . . . out on a limb . . . my good luck held and my old friend Kenneth Blackfan came to Boston and presided over the department with a splendid affectiveness for eighteen years.

Certain it is that the combination of Blackfan, the superb clinician and tactful administrator, and Gamble, the gifted investigator, each with full professorial rank, provided an unusual opportunity for both, as well as for all who were fortunate enough to work under them.

Free of administrative and clinical responsibilities but in close touch with clinical problems, Dr. Gamble continued "as an humble artisan" in the field of which he became the master. In the ensuing 30 years some 40 papers appeared, each meeting the standard of experimental design, execution, and presentation that has made them so unique in clinical investigation. His "Chemical Anatomy, Physiology and Pathology of Extracellular Fluid"[8] presents a compilation of his metabolic studies over these years with such clarity of thought, precision of writing, and artistry of exposition that it has become a standard text of undergraduate students, biological chemists, and teachers and practitioners of medicine. His economy of words in expressing with subtle humor wisdom derived from keen insight makes his lectures to medical students a further example of the art of medical science and gives to his companions a source of pleasure though at times misunderstanding, as when he commented to F. B. I. agents inquiring concerning his and my associations, "Why Dr. Butler is no more of a Communist than I am." Whereupon the gentlemen politely commenting, "That was all we wished to know," departed to make a report that Dr. Gamble has felt was the cause of some months' delay in his son's clearance for government work and, I believe, was the cause of my being subjected to loyalty-board investigations lasting several years.

Thus ends this brief sketch of the contributions and character of the individual we honor today. Little wonder that he is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, an Honorary Member of the Société de Pédiatrie de Paris, and a corresponding member of the British Paediatric Association; that he was asked to give the Thayer Lectures at Johns Hopkins in 1937, a Harvey Society of New York lecture in 1947, the Lane Medical Lectures at Stanford Medical School in 1949, the Chapin Oration for the Rhode Island Medical Society in 1950, and the Robert J. Terry Lecture at Washington University Medical School in 1952; that he was given the Honorary Degrees of S.M. from Yale in 1930, M.D. from Zurich in 1950, and S.D. from Chicago in 1952;

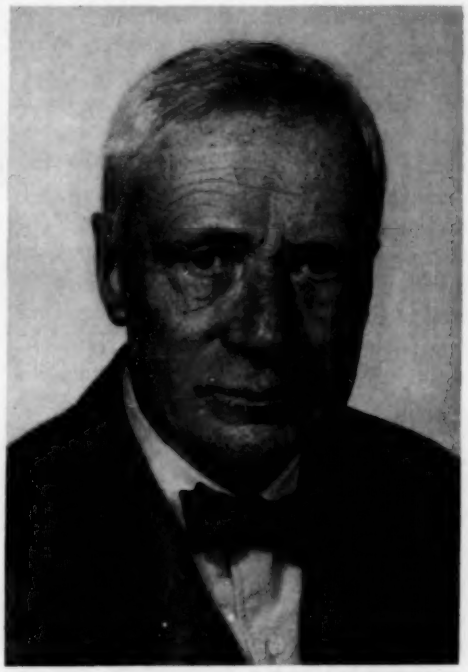

Fig. 1.—Dr. James L. Gamble.

and that he received the Borden Award of the American Academy of Pediatrics in 1946, the Chapin Award of the Rhode Island Medical Society 1950, the Moxon Medal of the Royal College of Physicians, London, in 1954, as well as the Kober Medal Award already mentioned.

Today, Dr. Gamble, knowing full well that public honors can never adequately express the affection and indebtedness felt by those to whom you have demonstrated the beauty of life in far more respects than extracellular fluid homeostasis, we, as individuals, thank

you for all you mean to us in delightful companionship, wise counsel, and scholarly inspiration, and we, as the American Pediatric Society, bestow upon you the John Howland Award for 1955 to pay honor to you for the contributions you have made by clinical investigation and graduate and undergraduate teaching to the health and happiness of people throughout the world.

ACCEPTANCE BY DR. JAMES L. GAMBLE

I am unable to find suitable words to express my pleasure in this award which comes to me from my friends over the years in the American Pediatric Society and which bears the name of one to whom I owe so much. He gave a young, ill-trained, would-be investigator place in his fine new chemistry laboratory and sustained his courage by a kindly disregard of his first fumbling efforts. This laboratory was, as you know, the first one in this country for study of disease in the clinic by quantitative methods of chemistry. It was the consummation of John Howland's clear vision of the value of such equipment in a university department of medicine. He brought a brilliant young biochemist from St. Louis to set it in motion. The ebullient McKim Marriott lost no time about this. Under the impact of his gay enthusiasm the laboratory immediately became importantly productive. Dr. Howland had a boyish pride and joy in his laboratory. He often worked there himself, carrying out some measurement which Marriott had assigned him. He enjoyed the challenge to accuracy of performance in a complicated analytical procedure and was greatly elated when he scored par on a theoretical solution. Those of us of the laboratory group at the Harriet Lane never thought of him as "The Chief." His attitude was that of an approving elder companion in the entertaining pursuit of new information by the methods of chemistry. We were expected to make our own choice of features of disease to assail by approach of our own devising. So there was in his laboratory a happy lack of program and a delightful spirit of free adventure.

The establishment of the laboratory came opportunely at the beginning of the era of micromethods of measurement which greatly facilitated examination of biochemical events in patients. Clinical medicine was being given a large new armament and it was exciting to find that these methods which were being developed by Folin, Van Slyke, and others made information we were after easy to come by. Moreover, we had in our midst a versatile inventor of micromeasurements. The study of the processes of acid-base metabolism during fasting, which Graham Ross, Frederick Tisdall, and I carried out, would not have been possible without the methods for measuring sodium, potassium, calcium, and magnesium which Benjamin Kramer's ingenuity gave us. The fruitful studies of rickets and tetany by Howland and Marriott and by Howland and Kramer were also implemented by these methods. I am glad to have this opportunity to acknowledge the laboratory's large debt to Benjamin Kramer.

In those primitive times the luxury of technicians for young investigators was unheard of. Marriot, however, did manage to provide himself with a technical assistant by an illicit arrangement. In the course of working out a method for measuring β-oxybutyric acid he became very bored setting up a battery of distilling flasks and then titrating the distillates. There was a bright 15-year-old Negro girl in the laboratory whose assignment was to wash the glassware. To our intense amusement McKim taught Topsy to perform this procedure and he boasted gleefully that none of "you chemists" could measure so near the mark as Topsy.

I must resist the temptation to further reminiscence of my years in this lush meadow of opportunity, else I will most certainly be felled by the gavel. They were filled with the pleasures of youthful enthusiasm and fine friendships.

It might be expected that having wandered so long in the region of medicine which we call pediatrics, I should offer you brief appraisement of the progress of our specialty. This I am unable to do. I have been a very unobservant wanderer, following a few pleas-

ant paths. By way of instance: Several years ago when I was still giving the medical students lectures, I received while on vacation a letter from Dr. Janeway in which, with gentle tact, he suggested that perhaps it was no longer necessary to use an entire hour of the students' time to tell them about rickets and tetany. I had polished my rickets and tetany lecture year after year and it had got to be, I thought, quite a good lecture. I gave it up with sincere sorrow over the passing of those two grand old diseases. So you can see that I am not competent to tell you what has happened to the content of our field in medicine.

Recent progress in knowledge of the organization of body fluids has also left me an astonished bystander. I had come to the naive belief that the behavior of the electrolytes followed a few simple postulations. Recent information has produced an increasing complexity of concept. I recall Lawrence Henderson once saying that he found it difficult to gain fluent command of new concept after he passed the age of 50. At any rate I am obliged to confess that I really don't know what the electrolytes are up to nowadays. But I have no grudge against complexity. It should be the physiologist's basal premise and the enduring incitement of his quest.

When the game has gone beyond one there is entertainment and profit in looking backward along the path of its development. On this pretext I shall relate a few bits of the history of fluid replacement therapy.[4] I especially wish to present to you, on this appropriate occasion, my favorite hero of British medicine, Thomas Latta. In the year 1832, Dr. O'Shaughnessy, a physician at Newcastle upon Tyne, sent to the editor of the *Lancet* his famous report of the results of his examination of the blood in cholera, in which he found large loss of water, neutral salts, and free alkali and accounted for these losses in the diarrheal stool (Fig. 2). Thomas Latta, a physician in the town of Leith near Edinburgh, who read his *Lancet* faithfully, at once set about applying these findings by injecting intravenously a solution containing sodium chloride and sodium bicarbonate. His first patient was an old lady severely sick with the cholera. The dramatic outcome of this historic adventure in therapy is recorded in a report which he sent to the *Lancet*. This report is a beautiful bit of writing. I can't resist reading it to you. He tells us that:

> She had apparently reached the last moments of her earthly existence and now nothing could injure her—indeed so entirely was she reduced that I feared that I would be unable to get my apparatus ready ere she expired. Having inserted a tube into the basilic vein, cautiously—anxiously I watched the effects: ounce after ounce was injected but no visible change was produced. Still persevering, I thought she began to breathe less laboriously. Soon the sharpened features, and sunken eyes and fallen jaw pale and cold, bearing the manifest impress of death's signal began to glow with returning animation, the pulse which had long ceased returned to the wrist and in the short space of half an hour, when six pints were injected, she was free from all uneasiness, actually became jocular and fancied that all she needed was a little sleep; her extremities were warm and every feature bore the aspect of comfort and health.

What a thrilling reward for bedside bravery! The full measure of my hero's courage came when this dear old lady died eight hours later. He thereupon decided that repeated injections must be given. During the epidemic he treated 16 patients who were near the edge of existence with injections as large as 2 or 3 liters and rescued 8 of them. A few other physicians ventured to try this bold new treatment and sent reports to the *Lancet* describing miraculous recoveries. So that in the year 1832 the life-saving effectiveness of replacement therapy was clearly recorded. Why did it fail of acceptance for nearly 100 years?

The answer is now quite clear. The quantity of fluid provided by physicians less resolute than Thomas Latta was inadequate. The urgency of the requirement for restoration of the volume of body fluid and for replacement of continuing losses was not realized. Indeed it was not until Marriott directly measured the large reduction of the volume flow of blood in dehydrated infants that circulatory failure was recognized as the immediately dangerous event and it became

EXPERIMENTS ON THE BLOOD IN CHOLERA.

To the Editor of THE LANCET.

SIR,—Having been enabled to complete the experimental inquiries on which I have some time back been engaged in Newcastle upon-Tyne, I beg you will have the kindness to give insertion to the annexed outlines of the results I have obtained:—

1. The blood drawn in the worst cases of the cholera, is unchanged in its anatomical or globular structure.

2. It has *lost a large proportion of its water*, 1000 parts of cholera serum having but the average of 860 *parts of water*.

3. *It has lost also a great proportion of its* NEUTRAL *saline ingredients.*

4. *Of the free alkali contained in healthy serum, not a particle is present in some cholera cases, and barely a trace in others.**

5. Urea exists in the cases where suppression of urine has been a marked symptom.

6. *All the salts deficient in the blood, especially the carbonate of soda, are present in large quantities in the peculiar white ejected matters.**

I am, Sir,
Your obedient servant,
W. B. O'SHAUGHNESSY, M.D.
London, 29 December, 1831.

Figure 2

clear that volume is the critical dimension of effective replacement therapy. With our present knowledge we can read Latta's report as a beautiful description of rescue from circulatory failure. We must suppose that his understanding of the processes of diarrheal dehydration was elementary. He simply accepted O'Shaughnessy's evidence of loss of water and sodium salts which obviously should be replaced and he learned at the bedside that the requirement is large and must be sustained. If the observations of this courageous Scotchman had been obeyed we would not have had to wait 100 years for replacement therapy. I will be very pleased if my British friends will someday see to it that my hero's portrait is placed in their Royal College of Physicians.

I like to think of Kenneth Blackfan as the Thomas Latta of our time. As Dr. Howland's perennial resident he watched over his patients with a devoted solicitude. He became convinced that infants dehydrated by diarrheal disease needed lots more salt solution than could be provided by subcutaneous and intravenous infusions. Dr. Howland had

seen intraperitoneal infusions used by Professor Garrod in St. Bartholomew's Hospital but was apprehensive of possible hazards to the patient. Blackfan begged hard and was permitted to try it. The importance of adequate replacement of fluid loss was convincingly demonstrated by a dramatic reduction of mortality which nowadays is sustained by continuous intravenous infusion.

With all respect for the laboratory approach, it is well for us to remember that large advances in medical science have been made and will continue to be made at the bedside by truly observing physicians. As in the story of fluid replacement therapy, judgement at the bedside can be the turning point of discovery.

34

1000 Gr. Serum.

Wasser	917,15		
bei 130° nicht flüchtige Stoffe	82,85		
Albumin etc.	74,43		
unorganische Bestandtheile	8,42		
Chlor	3,650	schwefels. Kali	0,218
Schwefelsäure	0,190	Chlorkalium	0,449
Phosphorsäure	0,226	Chlornatrium	5,677
Kalium	0,333	phosphors. Natron	0,444
Natrium	3,183	Natron	1,077
phosphors. Kalk — Magnesia	0,552	phosphors. Kalk — Magnesia	0,552
Sauerstoff	0,351		
Summe der unorganischen Bestandtheile			8,418

Dichtigkeit — 1,0261.

Figure 3

We will now return briefly to the laboratory to pay a bit of homage to a great chemical anatomist of the last century, whose work deserves at least a pat of recognition from modern students of body fluid physiology. Carl Schmidt was a pupil of Liebig and became professor of physiological chemistry at the University of Dorpat in Esthonia. Twenty years after O'Shaughnessy sent his report to the *Lancet,* Schmidt published a small book describing the chemical composition of the blood in healthy subjects and in cholera patients. He also analyzed the vomitus and the stools of his patients. He regarded the digestive secretions as transudates and was aware of the hazard to the chemical structure of the blood from wastage of these secretions by vomiting and diarrhea. His measurements from the blood serum of a healthy patient are recorded in the Table. The weights per liter, of the individual components, except for calcium and magnesium, which were measured together, are given in the left-hand column. This was 30 years before Arrhenius. Schmidt had never heard of an electrolyte. In those times the body fluids contained salts, not ions. So having measured the elements separately it was necessary to stick them together again in order to provide a suitable assortment of salts. His choice of salts is shown in the other column. We wonder how in the world he decided about this, why is potassium assigned to sulfuric acid and sodium to phosphoric acid? This is a good place to express our thanks to Arrhenius for permitting us to study the organization of body fluids on the basis of separately controlled concentrations of the individual ions, which so greatly simplifies our task.

Expressed as milliequivalents per liter, the values for the electrolytes of blood serum which we now accept as average normal are recorded in the first diagram in Figure 3. The values derived from Schmidt's measurements, obtained from a healthy subject by the ponderous methods of his time, are shown in the second diagram. As may be seen, his measurements were quite as good as ours, perhaps better. The diagram for the serum from one of his cholera patients describes correctly the distortions of the electrolyte structure characteristic of diarrheal dehydration, reduction of total cation, and, on the anion side, extensive reduction of bicarbonate and increase of protein from water loss. The basis for reparative therapy is clearly displayed. Unfortunately Schmidt was not a physician. There was no Thomas Latta at hand, and no application of his fine work was made. From Schmidt, the chemical anatomist, however, we learn a lesson in humility. Evidently life began before the flame photometer.

When in 1922 I came back to Boston at Oscar Schloss' request to help him get the new laboratory at the Children's Hospital under way, I had the immediate good fortune to be taken in hand by a third-year medical student who looked after me with great kind-

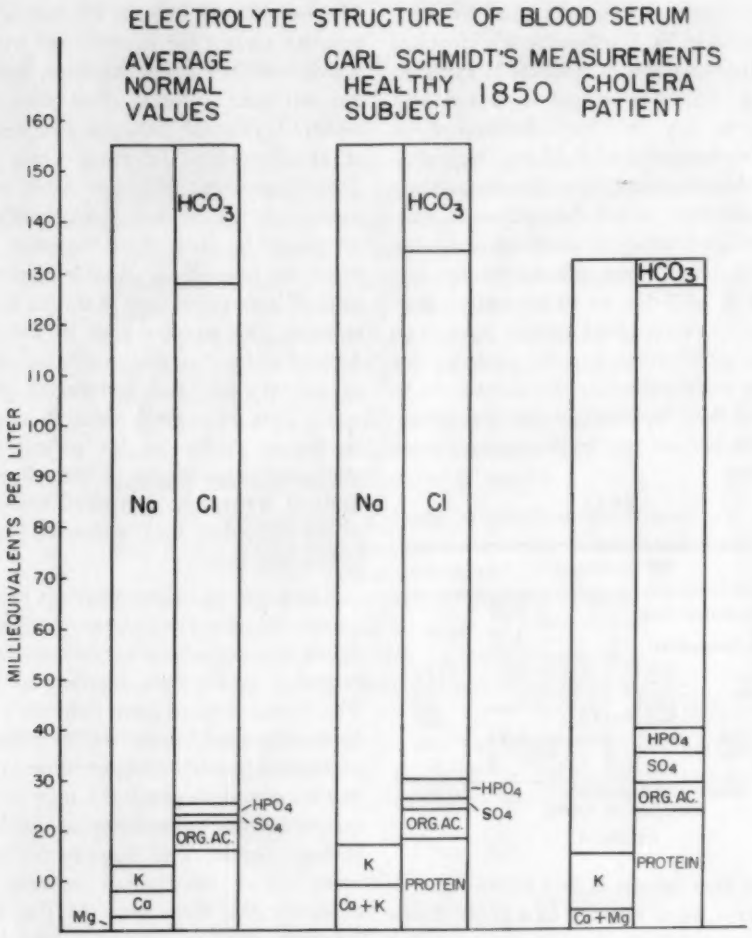

Figure 4

ness and provided me with encouragement over the next 18 years. He then left the Children's Hospital to become Chief of the Pediatric Department at the Massachusetts General Hospital, but his solicitude for my education continued. During the war years he asked me to participate in a splendid opportunity to study the states of fasting and thirsting which he had arranged with the Committee for Medical Research on the pretext of devising an emergency ration for castaways. He was, in the stern language of the Committee for Medical Research, the responsible investigator, so that my position on his team was delightfully carefree. I was given excellent data and had a very happy time making innumerable charts. So it is very pleasing to me that this dear friend and colleague was chosen to bestow the John Howland award.

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Society Transactions

AMERICAN PEDIATRIC SOCIETY, BRITISH PAEDIATRIC ASSOCIATION, THE SOCIETY FOR PEDIATRIC RESEARCH, AND THE CANADIAN PAEDIATRIC SOCIETY—SOCIETE CANADIENNE DE PEDIATRIE

Combined Meeting, Quebec, Canada, June 15, 16, 17, and 18, 1955

Human Growth, Development, and Adaptation: Address of the American Pediatric Society President. DR. ALFRED H. WASHBURN, Denver.

This paper was published in full in the July, 1955, issue of the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 2.

Autonomic Function in the Neonate and Psychosomatic Disease. LT. EARLE L. LIPTON (MC) U. S. N. R., DR. JULIUS B. RICHMOND, Syracuse, N. Y., and DR. SEYMOUR L. LUSTMAN, Chicago.

In any consideration of the etiology of psychosomatic disease, problems of multiple causation inevitably arise. Among these is the problem of basic biological predisposition to the development of such disease. Because psychosomatic disorders usually involve dysfunction of the autonomic nervous system, one of the predisposing etiologic factors to be evaluated is individual differences in autonomic function.

In order to shed some light on this problem a systematic investigation of variation in autonomic function among newborn infants has been undertaken. Initial observations involved measurement of skin temperatures (reflecting vasomotor reactive patterns) and cardiac rate (reflecting visceral activity) and responses of these functions to 13 stimuli, simulating conditions which an infant commonly encounters in daily care.

The experiments were performed on 16 male and 16 female normal newborn infants 2 and 3 days old in a constant temperature and pressure chamber. A thermocouple was placed on the dorsum of the left great toe and the temperature recorded by means of a constant-writing potentiometer. Heart rate was recorded on a standard electrocardiograph from two leads comfortably secured to the chest. The infants were nude, satiated, and allowed to accommodate to the environment until a constant skin temperature was reached.

Analysis of variance established that there are significant differences among individual babies for both heart rate and skin temperature responses to specific stimuli. A majority of the infants react in the same direction to specific stimuli. One infant responded maximally with both autonomic indices, others only with maximal skin temperature responses, and others with marked heart rate changes alone. Two infants reacted minimally in both autonomic functions. Two "hyper-reactors" responded maximally with either sympathetic or parasympathetic responses to different stimuli. Other specific observations relating to individual differences will be presented with detailed data and analysis. Some implications of these data for psychosomatic theory will be presented.

Behavior and Gastric Secretion: The Study of an Infant with a Gastric Fistula. DR. FRANZ REICHSMAN, DR. GEORGE L. ENGEL, and DR. HARRY L. SEGAL, Rochester, N. Y.

Physiological, behavioral and psychological observations were made on a 16-month-old infant with congenital atresia of the esophagus in whom a gastric fistula had been established on the third day of life. Over five months, during which she was hospitalized on the pediatric service, the child was studied in 59 experiments, each lasting two to four hours. Behavioral observations were recorded in detailed protocols by the experimenter who aspirated the gastric contents as well as by an investigator who observed through a one-way screen the child and her transactions with the experimenter. Approximately 600 specimens of gastric secretion were examined as to appearance, total volume, pH, concentration, and secretion rate of free and combined HCl and concentration and rate of pepsin secretion. Only the secretion rates of Total HCl will be reported here.

To correlate physiological and psychological findings, we proceeded as follows: We defined six affective states: two degrees of pleasure, joy and contentment; two degrees of anger, rage and irritation; depression; and depression-unpleasure. Similarly, we categorized into five degrees the child's interest in persons and things in her immediate environment ("object relations"), ranging from complete withdrawal into herself (Object Relation 1) to the most active exchange between her and the experimenter (Object Relation 5). The experimenter and the observer then independently graded from the written protocols affect and object relation during each of the periods of gastric aspiration, without knowledge of the chemical measurements.

Results.—The mean rate of Total HCl secretion (mEq/min.) during depression is less than one-half than that during irritation, contentment, and joy ($P<0.001$) and about one-fourth of the rate during rage ($P<0.001$). During rage secretion is significantly higher than during all other affects at the 1% or at the 0.1% level, except for the comparison with irritation, which is significant at the 2% level. There are no significant differences between the other affects.

In regard to object relations we found statistically significantly lower mean HCl secretion rates when the infant was withdrawn than when she related actively to the environment. During Object Relation 1 mean Total HCl secretion rate was significantly lower than during all other object relations ($P<0.001$). Differences between the other object relations were not statistically significant.

Thus, at this level of development, the secretion of HCl by the stomach is well integrated into the total behavioral activity of this infant. Affective states, be they pleasurable or unpleasurable, which are expressive of active communication with the outside world, are associated with rising secretion rates of HCl. The affect of "depression," in which communication with the environment is reduced or almost completely absent, is associated with decrease of cessation of gastric secretion. We regard these data as providing experimental support of the psychoanalytic theory of the oral phase of development.

DISCUSSION

Dr. Giulio Babero, Philadelphia: I have had the opportunity now to see this film three times, and I have almost become as much identified with this little girl as I am sure you have.

Actually, this is a remarkable technique in following one child and trying to classify some of the behavioral patterns. We really have not had very good methods of approach.

But I do think I should express a word of caution. I say this because of a patient we have followed for several years, with a similar lesion and of the exact same age. This particular patient, however, differs considerably in that she had a very warm home environment.

Little Monica, from what I know through previous and more lengthy descriptions, came from a very deprived, from a very neglected home situation, which was surely in no respect comparable to many of the children we seen in our pediatric practices. The little girl to whom I am referring actually had the reverse.

However, we were able to see in relation to some of the behavioral tones the effect of some of the changes which did occur in one experiment reported by Dr. Reichsman in respect to gastric secretion. Unfortunately, because of not being able to continue, we did this on a basis which Dr. Reichsman did not mention and apparently did not complete.

At any rate, we found that, following injections, the gastric juice came down from about a minimum of 25 cc. to somewhere around 2 or 3 cc.; that the viscosity became very high; that this gastric secretion, in terms of concentration in milliequivalents of HCl, was markedly depressed.

This, then, was somewhat different from the results reported by Dr. Reichsman, and perhaps points out that there may be differences, differences in response, which the paper of Dr. Lipton (which was not commented upon) shows, that there are differences in body responses to certain types of behavior.

Dr. Milton J. E. Senn, New Haven, Conn.: The authors are to be congratulated not only on their ingenuity, repeating in children experiments in psychosomatic relationships which were done earlier in adults, but also for providing one very important byproduct, namely, pointing out that what one does to children in the hospital, in terms of their general management, is very important, not only in affecting them psychologically, but also physiologically.

Whereas psychiatrists in the past have tried to point out the importance of changing the hospital environment satisfactorily, i. e., making it more humane, it has been very seldom proved to the pediatrician that what one does in the child's so-called routine management affects him physiologically.

I think Dr. Reichsman's lesson to us is that we must be aware of how we treat our children in terms of their relationship to physicians and nurses, lest we retard them psychologically and socially, leading to a condition which has been called hospitalism, or hospital anxiety.

DR. FRANZ REICHSMAN, Rochester, N. Y.: What was the age of the child Dr. Babero observed? Would he be good enough to say?

DR. BABERO: Sixteen months.

DR. REICHSMAN: That deprives me of the opportunity to say that the difference observed was due to differences in age level.

At the same time, I should like to emphasize that the previous experiences of the infants are indeed very important in the evaluation of such a study, and, without knowing those in detail—I am sorry I could not present Monica's previous experiences in detail here—one really cannot make a really good evaluation of what physiological and behavorial data mean in the context of such a study.

I am no surprised; I should not be surprised at all that, under different circumstances, different findings would be found.

This would not detract, I believe, from the implications of such a study, because it would remain to be seen what meaning the previous experiences had in conditioning the child behaviorally and physiologically.

The Pediatrician and Child Psychiatrist in a Collaborative and Supportive Role to the General Practitioner in a Rural Setting. DR. ANDREW D. HUNT JR. and DR. MORRIS PARMET, New York.

The material for this paper has been gathered in a setting where from the very outset a structure was defined which enabled the pediatrician, child psychiatrist, and general practitioner to test out certain concepts of practice. A "university type" of medical practice now exists in a rural setting. The rule of the specialists is to implement the central role of the family doctor and to provide those services that make for complete medical care. In the application of these services a continuing educational function is served which is expected to have its playback to the patient and the family through the medium of the general practitioner. The case material is selected because it points up the playback and the flexible interplay of the roles of the pediatrician, child psychiatrist, and family doctor.

Described in detail will be two cases of serious constipation simulating megacolon. The first case, treated by us early in our Hunterdon County experience, was admitted to the hospital while his general practitioner was away on vacation. Advice given by this man, as obtained during the history, to the parents of the child during the preceding few years, had been naive, authoritarian, and, in some instances, destructive. In our final case conference, the family physician became involved in the discussion, and took an active part in it. This child meanwhile was responding well to treatment.

The second child was referred to us by this same physician during our second year of operation. The symptoms were most similar to those in Case 1, as was the age of the child. He was hospitalized in the pediatric service, megacolon was ruled out radiographically, and several conferences were held with the parents around possible emotional and personality relationships. The parents developed a modicum of insight into the possibilities of an emotional etiology for their child's problems and determined to discuss the matter themselves and eventually to call for an appointment to the child guidance service.

About three months after the child had been discharged, the family physician paid us a visit and reported on the child's progress; constipation had ceased to be a problem, and the physician had noted a change in the child's attitudes which he was now able to recognize as being favorable and desirable. The physician had been able to support the parents in dealing with increased aggressiveness on the part of the child, and, in general, his counselling now was constructive, intelligent, and enlightening.

An interview with the parents at this point revealed that they had acquired more understanding of their problems and were able to see similarities between this situation and their relationships with their own parents. In our estimation, the case had progressed sufficiently that there was no longer need for referral to the child guidance clinic.

DISCUSSION

DR. JULIUS B. RICHMOND, Syracuse, N. Y.: I want to congratulate Dr. Hunt and his collaborator for pioneering in a very interesting setting in a very interesting way.

One could comment in a variety of directions in relation to this presentation because it does raise many interesting points.

First, I should like to indicate, in relationship to the problem of constipation (which the pediatrician so frequently encounters in his practice), that certainly he is in the best position to play a prophylactic role.

I should like to emphasize that there are various degrees of constipation; minimal constipation being on one end of the spectrum and megacolon and fecal soiling on the other, the latter constitutes a serious problem in psychopathology, and certainly socially, in terms of the child's attendance at school, his management in the family, in play, and so forth.

I should like to raise a question concerning whether this group has made any plans to deal with the aggressive behavior of the children they have treated. We have found this to be very difficult; we have found it a problem to the parents, who have been accustomed to a very placid child and have certainly found it very difficult to deal with the change in behavior.

The other point I should like to raise as a question to Dr. Hunt is this. It is an obvious one, but I wonder if he might make a comment on it. He deals with two instances in which there has been considerable effectiveness on the part of the group. I wonder if he might want to say something about the rather considerable resistance which sometimes develops because of the personal feelings of physicians in relation to dealing with psychological problems.

DR. HARRY F. DIETRICH, Beverly Hills, Calif.: I should like to ask two questions.

If I understood correctly, I am a little bit concerned with the economics of having 12 full-time specialists taking care of what is thrown to them in a county of 45,000 people. I would like to ask who pays for that and whether it is considered to be a fundamentally sound economic procedure. I think, from a standpoint of postgraduate medical education, this is a very interesting experiment; but I should raise the question of the wisdom of attempting to extend it over any great part of the country.

I should also like to ask the reaction of the general practitioners in the community to calling in a specialist.

DR. HUGH E. MCCULLOCH, Chicago: I should like to support Dr. Hunt's presentation by our own experience at our new sanitarium in dealing with the general practitioner, in this case with a specialized disease instead of the general practice of pediatrics.

In the past five years, we have accumulated about 800 families, but about this same relationship has been worked out. I noticed that Dr. Hunt said "seemingly on a satisfactory basis." He has qualified it to that degree.

In this case, we have assumed that the general practitioner does not often see a young person in the adult stages of rheumatic fever in his general practice, and we have assumed also that these patients need long-continued care in order to prevent progressive rheumatic heart disease.

DR. EDWARD RABE, Danville, Pa.: In the last three years or so, we have had somewhat similar experience to that of Dr. Hunt's, the difference being that we are practicing in a hospital which is closed-staff and is set up without the collaboration, as you might say, of surrounding physicians. We draw from a radius of approximately 60 miles.

We have been making efforts to educate and to help the physicians in the area care for children. We have found, similarly to Dr. Hunt, that we have the greatest resistance in trying to educate the physician, the general practitioner, in aspects of preventive behavorial pediatrics, so much so that we have had to cease sending out verbatim copies of the psychologists' reports; they have been so misunderstood.

The second thing I wish to mention is that the greatest educational process which we have found, or the most effective, is twofold in such a situation: (1) the letters which go out to the physicians from the cases which they have sent in; and (2) the interns, with whom we have had only four to six weeks' experience, who have gone then into the surrounding communities as general practitioners.

DR. SAMUEL M. WISHIK, Pittsburgh: My comment pertains not so much to the primary purpose of the paper on educating general practitioners, but to techniques of measurement.

As a pediatric profession, we have broadened our scope of interest, as Dr. Washburn indicated in his presidential address; and we have reached a stage of questioning the statistical significance of our experimental work. Now it seems necessary for us to open our minds to the possibility of using sophisticated mathematics in measuring the effectiveness of our pediatrics as its scope is broadened.

While we accept the possibility of measuring pulse rate and other physiological changes such as the first two papers indicated, we raise a quizzical eyebrow when one talks of measuring, for example, how much a mother forces food on her child.

I think we should be receptive to the techniques, not new any more, of such social sciences as psychology and sociology, some of the scales (such as the Lazarsfeld and Guttman scales) which would help us measure the nonorganic emotional reactions of children, the attitudes of parents, and also the receptiveness of professional people to new methods of education. As we broaden our scope of interest, we should also broaden our measurement techniques in evaluation.

DR. ALLAN M. BUTLER, Boston: I wish Dr. Colin C. Stewart were here to add to this discussion by giving the experience of the Hitchcock Clinic, in Hanover, where a similar thing has been going on over a period, I suppose, of 25 years.

In answer to Dr. Dietrich's comment, that clinic has far more than 12 full-time physicians; and I should assume the area within a twenty-mile radius perhaps includes 50,000 people.

That clinic, with that size of staff, has had great success raising the standards of medicine in the area and has been successful financially.

DR. REGINALD LIGHTWOOD, London: I am sure that those who come from England will feel very attracted by what Dr. Hunt has been describing to us this morning.

In England the circumstances of practice are very much as he has described, where the pediatrician is called as a consultant to help the general practitioner, who is general practitioner in the wider sense and is responsible for his patients and wants help in diagnosis.

Very often in a domiciliary consultation, the management which the consultant is able to suggest means taking the child patient into the hospital. But in a scheme which has been started on an experimental basis at St. Mary's Hospital, London, we have been able to show that admission to the hospital is frequently not so essential in this sort of work as it would appear to be or has been thought to be in the past. In this scheme we are attempting to provide the sort of service which Dr. Hunt has been describing in an urban community with high population density, worked within a radius of approximately two miles from the hospital center. While always maintaining a standard of medical care as high as that of the hospital, we aim to provide in selective cases the services of investigation, diagnosis, care, and treatment without admitting the patient.

The question has been asked whether the work described by Drs. Hunt and Parmet is economically sound. I do not know what the answer is for a rural community such as has been described by Dr. Hunt; but I can say that, when an urban community such as the one surrounding my hospital in London is served, the cost works out very much more cheaply than hospital care. Certainly the economic comparison is not a simple one, overhead charges remaining, but, as far as we can tell from our calculations, we do the same sort of thing at less cost, maintain the same standards of care in selected cases in the home, and keep the family doctor in charge of the patient. That, I think, is most important.

When we started this scheme, rather more than a year ago, we thought rather glibly in terms of helping the family doctor, as well as the patient, of course, and that we were going to help in his education, keeping him up to date. But, in view of the differences between hospital and domiciliary practice, you will not be surprised at all if I mention that what we have found is that we are educating ourselves. The team consists of trained pediatric personnel, doctors and nurses, and this small team who do this home-care work for sick children find that it is of real educational benefit to themselves, which we hope to be able to pass on indirectly to our students in teaching.

DR. ANDREW D. HUNT JR., New York: On Dr. Richmond's question about plans to deal with the aggressive behavior of these children—I wish Dr. Parmet were here to discuss them—actually, in the first case, the mother, because of the way our child-guidance service operates, was

seen weekly by the psychiatric social worker at the same time the child was seen by Dr. Parmet; and presumably most of her function was in helping the mother deal with these problems.

In the second case, this seems to have been handled quite adequately by the family doctor, because I saw that mother and child twice in follow-up, and she felt that she was coping by herself. She had considerable understanding in the problem, and seemed at that point to be able to handle the situation on her own.

Dr. Dietrich's question, of course, brings up the whole problem of this kind of operation and has been of some concern to us.

At the present, the group is just about breaking even. Perhaps the reason this is possible is that each specialist chief of service receives from a professional-service fund into which all fees are deposited.

All group members have subscribed to this philosophy of practice; one which is, after all, not totally revolutionary.

We have some foundation support from the Commonwealth Fund, on a gradually decreasing basis, so that the complete success of the financial aspects of this cannot be answered at this point; but, after two years of operation, our group indebtedness has decreased from approximately $28,000 to $3000, which represents considerable improvement and augurs well for the future.

Dr. McCulloch's question certainly brings up a problem in what to do with patients who require long-continued care. So far, we have been able to work out a rather friendly relationship with the family doctor, so that we can supervise these patients after they go home by remote control or have them come back in to see us at frequent intervals. Generally speaking, most of these problems are handled amicably.

I want to thank Dr. Rabe. We are extremely fortunate as far as house staff is concerned. We have interns rotating out from two New York hospitals; we have a pediatric resident sent out to us by Dr. Holt, and we have medical students from three medical schools who serve as junior interns. The house-staff situation is quite ample. House officers do, as Dr. Rabe says, provide a vast amount of the postgraduate education.

I certainly thank Dr. Wishik for his comments and Dr. Butler for his. The Hitchcock Clinic is something which we have often talked about; we should like to go up to see it, because we know it is somewhat similar and the operation they have has been extremely successful.

Certainly, Dr. Lightwood's comments were most gratefully received. Thank you very much.

Observations on "Unexplained" Chronic Diarrhea in Early Childhood. Dr. Dane G. Prugh and Dr. Harry Shwachman, Boston.

In the course of studies of gastrointestinal disorders in infancy and childhood, a group of cases has been identified which show continuing diarrhea related to psychophysiologic disturbance in gastrointestinal function. Symptoms tend to appear after the first six months of life and to continue at least into the second or third year. These cases appear to be distinct from idiopathic celiac disease, without the gastrointestinal absorptive defect and the metabolic reverberations which characterize that illness. Localized structural change, as in prolonged ulcerative colitis, does not occur in these patients, and careful physical and laboratory studies reveal no local or systemic abnormalities of immediate etiologic significance. Dietary and other traditional methods of treatment have been of limited value in the management of this type of disturbance. Present studies indicate that diarrhea in this group of infants and small children tends to appear in settings of family crisis or in relation to exacerbations of emotional conflict on the part of parents, with associated changes in the handling of these children. Genetic and somatic factors, such as the pattern of inherited autonomic response to stress and incidental physical illness involving the gastrointestinal tract, appear to play a role in the predisposition to these disorders.

A group of 20 cases is presented, exhibiting diarrhea of the kind described. Detailed observations are summarized regarding the type of predisposition in child and parents, the precipitating factors operating to disturb "emotional homeostasis," the nature of psychophysiologic derangements, and the family circumstances which appear to lead to perpetuation of these disorders. Charts are employed to indicate correlations between significant psychologic and physiologic data. A program of pediatric management, involving a supportive psychological approach, is described, which can lead to successful resolution of this symptom picture.

DISCUSSION

DR. ALAN MONCRIEFF, London: It is a habit, in the British Paediatric Association to be quite rude to each other in a very friendly way; and no one will accuse me, I think, of not having great sympathy with psychological implications of diseases of childhood.

But the sort of remark we would make at this stage in one of our own gatherings, I am quite sure, is not beyond the lines of what actually happens when, after a paper of this sort, an elder statesman got up and reminded us that, after the height of the storm, there came out of the burning bush a still, small voice which said, "Fiddlesticks!"

I did not really get up to remaind you of that, but of the well-known syndrome known in our lives as "examination diarrhea." That will remind us, of course, that there are psychological factors involving bowel disturbances.

Likewise, I should like to switch the emphasis to a different aspect of this unexplained diarrhea, and to ask the Boston group particularly with regard to the possible cure of fibrocystic disease in a spontaneous way. I have had two cases in the last two years which we regard as fully established examples which, nevertheless, proceeded to spontaneous cure. We can only conclude there was a later appearance of the enzymes.

I think we tend to assume that the gastrointestinal enzymes come and are established and remain in full force for the rest of the child's life. I am coming to believe that this is not necessarily true. I believe the time for the appearance of enzymes varies in different children.

Dr. Armand Delille years ago pointed out that if you feed starchy food to a very young baby, starch granules appear in the stools for a matter of days and then disappear. It can only be assumed that the enzyme appears as a result of that stimulus.

One wonders also whether the cure of such a syndrome as infantile renal acidosis also represents the later appearance of an enzyme which ought to have been there from the start, to deal with the particular renal function involved.

One also wonders what is the effect of temperature upon these enzymes that, with a rise in temperature, you pass beyond the zone of enzyme activity and, in consequence, diarrhea appears.

I am just wondering whether some of these bouts of diarrhea might not have an explanation on that basis rather than entirely upon the psychological explanation which has been offered to us.

DR. ALTON GOLDBLOOM, Montreal: In an ancient book, "The Golden Ass," written by Lucius Appulius, the hero, through witchcraft, is transformed into an ass; he relates one of his experiences in which he was purchased by a lady who treated him very cruelly by beating him unmercifully over the rump, when he took his revenge in the only manner at that time open to him.

We have, in the American language (perhaps in the English, too), introduced gastrointestinal terminology to indicate our emotions. We say that a certain fellow nauseates us, or that another one gives us a pain, which is not always in the neck.

We are familiar with people, as Professor Moncrieff has indicated, who suffer from examination diarrhea, and others when obliged to appear before large audiences (such as famous artists), who suffer from either nausea or diarrhea before an important concert; so that we are familiar with gastrointestinal phenomena as responses to the emotions of adults to an extent which, I say, has become part of our language. It is therefore only natural that we should eventually come to recognize the same in children. As always in children, the responses are greater with less stimuli.

I feel grateful to Dr. Prugh and Dr. Shwachman for having brought to our attention, through the scientific observations which they have made in Boston, phenomena which are, I am sure, familiar to most pediatricians of experience.

DR. HARRY H. GORDON, Baltimore: It gives me pleasure to note that Dr. Shwachman is co-author of this paper, because this indicates that he too does not begin study of an infant with chronic diarrhea by duodenal intubation.

I wish to ask Dr. Prugh whether, in any of the patients, the beginning of the illness might have been as an infectious diarrhea.

During World War II, a large number of soldiers were sent back to the zone of the interior from overseas theaters with chronic or recurrent diarrhea. Their illnesses had obviously begun as infections, some as proved Shigella or amebic dysentery, others as febrile bouts of bloody diarrhea without identification of etiology.

On return to this country even with very intensive laboratory studies, we were unable to turn up evidence of continuing infection. As these soldiers were watched over a period of time, a variety of factors precipitated recurrences.

Sometimes, diarrhea heralded an attack of malaria, coming one or two days before the actual malarial attack; in others, very hot weather would precipitate an attack, in still others an alcoholic debauch.

In a goodly number, notification to the soldier that he would shortly return to full duty precipitated an attack, thus indicating the importance of unadulterated psychologic factors.

DR. ANDREW D. HUNT JR., Flemington, N. J.: I do not believe Dr. Prugh needs the support of a country doctor in this discussion; but we have just lived through the experience, in our hospital, of a baby with diarrhea, a terribly sick baby; yet laboratory investigations revealed no disease.

The family situation is one of these extraordinarily grotesque ones, which we will not bore you with now. The mother was strongly opposed to this baby, and there were many evidences of gross rejection.

The interesting part of the whole course of this infant has been the feeling of my chemically-trained resident who is firmly convinced that this problem is mostly on a psychological basis; indeed I have trouble inhibiting him in his concept.

I think that the thing I took out of Dr. Prugh's discussion was not that the evidence is absolute that these cases are completely caused by emotional tension, but rather that we should accept the fact that social information such as this, parent-child relationships, may be as truly data in the evaluation of a baby's disease as are the blood chemistry and the stool trypsin.

The true significance of such data is still open to question; but the possibility does exist that there is a strong relationship between these kinds of situations and gastrointestinal disturbances in infants.

DR. JULIUS B. RICHMOND, Syracuse, N. Y.: I found this paper very interesting; and I should like to make a comment or two concerning Dr. Moncrieff's comments.

First, I wonder if Dr. Prugh might tell us something about the laboratory data which was obtained on these infants—I know that, because of the pressure of time, he passed over it rather hurriedly—because I think this does relate to the comments which Professor Moncrieff made.

I think it might be well to recall that, a number of years ago, Drs. Gibson and Phillipsborn, of Chicago—I do not think either of them is here—reported in *The Journal of Pediatrics* that there is generalized depression of all pancreatic-enzyme secretions in marasmic infants. They studied several such infants and, during the period of marasmus, found that the illness of these babies could be confused with mucoviscidosis, because of the fact that there seemed to be relatively low enzyme concentrations.

However, as the nutrition of these infants improved, and they studied them serially over a period of time, they found that the enzyme values returned to normal. Therefore, if we can relate this to Dr. Reichsman's report this morning concerning HCl secretion, I think the implication is that, certainly, psychological factors could be associated with relatively low biochemical values in relationship to the enzymes.

DR. DANE G. PRUGH, Boston: I should like first to thank Dr. Moncrieff for his certainly heartfelt and penetrating observations.

We anticipated a certain healthy skepticism, for which I congratulate Dr. Moncrieff. The course of science demands such skepticism.

I should like to point out, however, that no statement was made that the phenomena described were wholly due to emotional factors. We regard the gastrointestinal tract as the final common pathway upon which noxious stimuli of various natures may act, including somatic and emotional ones. The specific psychophysiologic interrelationships are not clearly demonstrable at this point. More exact measurements of changes in various modalities of lower gastrointestinal function have not yet been possible for us. We have used fluoroscopy and other methods of study, but more satisfactory techniques are being developed at the present time.

We have tried to emphasize that etiology, as we saw it, was multifactorial in nature, and that possible genetic factors, emotional factors, and incidental somatic ones appear to be involved.

The influence of occasional respiratory infections or of infections of the lower intestinal tract upon the appearance of diarrhea in these children certainly did seem to be of importance, as

Dr. Gordon pointed out, and did seem to be associated in certain instances with the onset and exacerbation of the illness. This again to us would represent additional evidence that the lower bowel can respond in a nonspecific way to various stimuli, especially in a child predisposed by a variety of factors to this type of gastrointestinal response.

I should like to thank Dr. Goldbloom for his preceptive remarks, and Dr. Washburn as well. In response to the questions raised by Dr. Moncrieff and Dr. Richmond regarding the detailed laboratory data, particularly those related to pancreatic enzymatic function, I should like to ask Dr. Shwachman, if he is present, to comment, since he is the person who knows most about this particular phase of this collaborative study.

DR. SHWACHMAN, Boston: I should like to thank all those who have made comments concerning this paper.

Patients with demonstrable organic conditions were eliminated from the group of patients reported. This includes a few patients in whom a Salmonella infection may have been the precipitating factor.

In reply to Dr. Moncrieff I believe the question concerning pancreatic function does not bear directly on the presentation. I can reply that we have not encountered a return to a normal pancreatic enzyme level (amylase, lipase, trypsin) once we were certain that we demonstrated complete pancreatic insufficiency. This experience covers approximately 2500 duodenal assays. However, we have had a number of referred patients diagnosed as having mucoviscidosis on the basis of the clinical picture and the demonstration of absent trypsin in the duodenal fluid, only to find a normal duodenal fluid when the patient was subsequently restudied by us. We have tried to avoid the greatest error, which lies in the manner of collecting an adequate duodenal fluid. In our institution a special laboratory has been set up which is responsible for the collection and assay of the duodenal fluid. In this way the experienced personnel avoids many of the pitfalls which beset the busy resident who has had little or no experience in collecting adequate duodenal fluid specimens.

A test of great diagnostic value has been of special interest to us, namely, the study of sweat sodium and chloride following a mild thermal stimulus. From a study of over 600 patients this past year by a simple technique we feel that the diagnosis of mucoviscidosis can be made more readily and with less discomfort to the patient than the more difficult duodenal assay.

In reply to the question as to the depression of pancreatic enzyme activity with infections and severe malnutrition per se, we have not been greatly impressed. A number of patients with severe malnutrition and "toxic" states studied by us have not shown a uniform diminution in enzymic activity. However, a small number of patients have shown diminished activity with a return to normal activity accompanying restoration of health. Veghelyi, of Budapest, claims a reduction of pancreatic enzyme activity in scarlet fever and other toxic conditions.

I should like to say a word about two patients in whom the diagnosis of mucoviscidosis was made and referred for confirmation of diagnosis and treatment. In Case 1 the mother lost her first two girls with mucoviscidosis in infancy and was greatly concerned over her fourth child, a boy, who failed to gain and had chronic diarrhea. Child 3, a girl, was found to have mucoviscidosis and was progressing satisfactorily with therapy. Mother was convinced that her boy had mucoviscidosis in spite of our contrary opinion (backed by doudenal fluid study and sweat test). It took nine months of reassuring care to this mother before she fully realized that her boy was a healthy boy.

The second case was that of an infant who had chronic diarrhea and repeated respiratory infections and came from a clinic which stated the boy had pancreatic fibrosis. The duodenal intubation was stated to show no trypsin. The mother tended to be an unreliable, hysterical, attention-seeking individual who ran away from home at age 16 and married and had her first child at 17. She separated and remarried a number of years later, and at 25 had the boy who presented the diagnostic problem. His symptoms fit well with the clinical impression of pancreatic fibrosis, but all our studies were normal. Both patients showed an excellent clinical response and are mentioned to indicate that occasionally a diagnosis of mucoviscidosis is made, when in fact we are dealing with essentially an emotional problem.

The group of patients presented does not represent a new clinical entity, as Dr. Goldbloom pointed this out. This condition is much commoner than we have indicated by the number of cases reported. Dr. Prugh did not have time to indicate that complaints other than diarrhea

exist, such as feeding and sleep problems. Finally I should like to point out that the majority of these children with diarrhea, and their parents, can be successfully managed by the pediatrician, and only rarely will it be necessary to turn to the psychiatrist for help.

Studies on the Pressure and Motility Patterns of the Distal Colon of Children in Health and Disease. Dr. Murray Davidson, New York.

There is a paucity of information concerning intraluminal pressures and motility patterns in the gastrointestinal tract of children, although this subject has been extensively studied in adults during the past 30 years.

Concurrent pressure tracings from various loci of the distal colon were made by means of a tandem system consisting of a Sanborn Poly-Viso Recorder and three Sanborn electromanometers attached to open-ended tubes in the bowel lumen. The subjects ranged in age from infancy to 13 years, and the studies lasted from 30 to 180 minutes. The position of the tips of the catheters was checked by fluoroscopy. The results of 40 typical normal recordings will be discussed and differences in wave patterns of closely related segments of the lower bowel, heretofore not described even in adults, will be shown. Areas of similarity and difference between these tracings and those in adults will be compared. The effect of sleep and ingestion of food on intestinal motility will be demonstrated.

The results of similar studies on children with acute diarrhea, childhood ulcerative colitis, and congenital megacolon will also be presented. In addition the usefulness of this technique for evaluating the efficacy of pharmacologic agents will be highlighted by demonstrating the production of diarrheal wave forms following the feeding of magnesium sulfate to normal subjects.

The Effect of Prolonged Cortisone Therapy on the Statural Growth and Skeletal Maturation of Children. Dr. Frederic M. Blodgett, Dr. Domenic Iezzoni, Dr. Donald Gribetz, Dr. Leo B. Burgin, and Dr. Nathan B. Talbot, Boston.

This paper summarizes observations on the influence of orally administered cortisone upon the statural growth and skeletal maturation of 26 infants and children who have been studied for periods of from six months to four years. This group includes 11 patients with congenital hyperadrenocortical virilism, 8 with severe asthma or eczema, 2 with hypocaloric dwarfism, 4 with primary hypopituitarism, and 1 with primary hypoadrenocorticism.

The data obtained show that administration of cortisone slowed both rate of growth in stature and rate of skeletal maturation, the latter usually more than the former. The slowing of linear growth became evident within 1 to 3 months and the retardation of skeletal maturation within 6 to 12 months after therapy was started. While the degree of decrease in these rates appeared to be directly proportional to the dose used in all patient categories, the absolute dose needed to cause marked slowing of growth differed markedly from group to group. The dose needed to produce an approximately 50% reduction in growth rate was least (about 10 mg. per square meter per day) in the hypopituitary and greatest (up to 250 mg. per square meter per day) in the allergic infants. Following reduction or discontinuation of cortisone dosage, there was a tendency for rates of growth and maturation to rise toward or above pretreatment levels. As a result of this, many of the patients were able to regain during periods when therapy was reduced or discontinued much of the ground lost while on treatment.

Viewed as a whole, the data indicated that while cortisone may cause marked stunting of growth during the period when it is being administered, this may not result in a reduction in ultimate stature. Indeed, study of height age-bone relationships reveals that 18 of the 22 patients who were given cortisone alone showed a gain in height age relative to bone age during the period of therapy, a change which if maintained should result in an increase in ultimate adult stature. This change appears to have been due, in the case of the adrenocortical virilism patients, to suppression of production of pathologic adrenocortical androgens which cause bone age to advance more rapidly than height age. In some of the allergic and dwarfed patients who were underweight for height, improvement in height stature during cortisone therapy appeared to be referable to marked improvement in appetite and hence body Calory stores.

It is concluded that the temporary growth and maturation suppressant effects of cortisone do not necessarily contraindicate the careful administration of this agent over considerable periods of time to children with conditions likely to be benefitted by its use. In the case of the

adrenocortical virilism patients, a favorable outcome as regards stature appears to be dependent upon continuous cortisone therapy. By contrast, in the other types of patient, it appears essential to discontinue therapy from time to time.

Fat Children Grown Up. Dr. Hilde Bruch, New York.

During 1953-1954 follow-up observations were made on former fat children who had been studied from 1937-1940 at the Babies Hospital and the pediatric department of Vanderbilt Clinic. All fat children who had come to the attention of the different clinics at the Medical Center during that period had been included in the original study. Follow-up letters were sent to 113 fat boys, but the majority were returned as unclaimed. Only 42 received the follow-up notices, and of these, 24 young men, or 57%, came for a follow-up visit. Of the 112 fat girls, 32 were reached by a follow-up letter, but 10 responded to it. The following report is based on the later development of the 24 fat boys.

The earlier study had shown that the then current concepts on endocrinologic etiology of obesity were erroneous. At the same time it was noticed than an intense emotional involvement of the parents, usually the mother, with the child, led to overfeeding and overprotection. The resulting overeating and inactivity gave a seemingly simple explanation for the development of obesity. There was strong psychological resistance against changing the faulty habits.

The follow-up study was designed to determine whether the adult adjustment, both in terms of weight and of emotional development, could have been predicted on basis of the medical and psychological findings in childhood. If one evaluates weight and emotional adjustment as independent variables, four possibilities exist for their combination, namely, that of slenderness with good adjustment, slenderness with poor emotional adjustment, continued obesity with good adjustment, and continued obesity with maladjustment. All four combinations were observed in this group, with the last group having a subdivision of obesity with frank psychotic development. The reevaluation of our early data in the light of the outcome in young adulthood leads to the conclusion that a detailed history of the physical and emotional development of an obese child and his family relationships permits a fairly accurate prediction of the future course.

It is important to note that therapeutic interference, particularly dietary restriction, did not influence the long-range weight development; in some cases it had become the focal point of serious emotional problems. The effect of endocrine treatment was even poorer. Although psychiatric disturbances had been recognized early in many instances, adequate psychiatric treatment had not been carried out in these cases because of resistance against the intensive work that would have been required for the fat child and the involved parent.

A Six-Year Study of the Epidemiology and Control of Staphylococcal Skin Infections of the Newborn. Dr. A. F. Hardyment, Dr. R. A. Wilson, and Dr. W. H. Cockcroft, Vancouver, B. C., Canada.

With the introduction of individual nursery technique and of antibiotics there was hope that staphylococcal infection would be controlled. In fact, however, several strains of staphylococci are resistant to most antibiotics, and skin infections remain a stubborn problem in many hospitals.

When this problem affects a hospital nursery, the following questions should be asked by those responsible.

1. Is the incidence of skin infection higher in our nurseries than elsewhere?
2. What skin lesions of the newborn are to be considered ineffective, and what lesions are to be considered irritative in origin?
3. What is the causative organism, and what are its characteristics?
4. Where is the reservoir of the causative organism
   (*a*) Mothers, or other ward visitors?
   (*b*) Nurses, doctors, or other hospital personnel?
   (*c*) Other babies in the nursery?
5. How does the organism reach the baby's skin
   (*a*) By droplet contamination?
   (*b*) By direct contact with the contaminated hands of mothers or attendants?
   (*c*) By contact with contaminated fomites?

6. Is the prevalence of skin infection in a nursery affected by
   (*a*) Crowding?
   (*b*) Number of nursing hours available to the babies?
7. Are newborn babies with skin infection more often nasal carriers of the offending organism than babies who do not have skin infections?
8. Are pyogenic staphylococci present on the skin of the normal newborn baby?
9. What methods of control are efficient, practical, and inexpensive?
10. Does a technique which is efficient in reducing the number of skin infections in the nurseries continue to prevent staphylococcal infection after cessation of treatment upon discharge?

Since April, 1949, the authors have sought answers to the above questions in the nurseries of the Vancouver General Hospital, where 4500 babies are admitted each year.

For the purpose of this study, any skin lesion greater than 1 mm. in diameter and from which the Staphylococcus pyogenes can be cultured has been considered a pustule. Cultures were obtained by withdrawing pus from an intact pustule with a sterile Pasteur Pipette.

The Staphylococcus pyogenes has been identified by its cultural characteristics, phage type, and antibiotic sensitivity.

To establish the basic epidemiological pattern in our nurseries, control observations were made for three years (April, 1949-May, 1952).

We observed the following: incidence, effect of crowding, degree of air contamination, age of the infant at onset, and carrier rates among babies, mothers, and personnel. From May, 1952, until September, 1954, the effects of various methods of skin care were studied. During this period, one-third of the infants were continued on the original method of skin care, as a control group.

Between September, 1954, and the present, no medication was applied to the infants' skin. For part of this period, attendants washed their hands in a 0.3% solution of hexachlorophene in green soap. For the remainder of this time, the hand wash was a 3% solution of hexachlorophene in chemical detergent.

In order to discover if a method of skin care which is efficient in the control of skin infections in the nursery will continue to prevent skin infections after cessation of treatment and upon discharge of the baby from the hospital, a survey was carried out of 10,000 babies visited in their homes during their first six weeks of life. These were babies discharged from all the hospitals in this area, but 3125 of them were from the Vancouver General Hospital.

From the evidence collected in the foregoing experiments our original questions are answered in part. This evidence will be presented in detail.

DISCUSSION

Dr. Clement A. Smith, Boston: I think it is too bad that, although this is such a pleasant place to meet, Dr. Hardyment's nursery is about 3000 miles away and our nursery is 350 miles away and each of us have to take what the other tells him on faith.

We certainly are satisfied with skin care of our infants (as Dr. Allers and Dr. Hubbell and Dr. Clifford sometime ago arranged it), without application of drugs or soaps to the skin and with particularly careful attention to the scrubbing of nurses' and doctors' hands. They scrub with a lotion of G-11 and with specially sterilized brushes.

I have known about the work of Dr. Hardyment for a long time, and I am glad to have it presented as one of the few studies large enough to throw light on this problem. I can't help but wonder whether we would agree that these infants have true pustules. Even though the babies are carrying these bacterial organisms in their noses and on their blankets, which would make it seem highly probable that you would get the same organism by culturing the skin, I can't help but wonder whether these organisms would start pustules in the skin of other infants.

I hope that anyone else who has had experience, one way or another, with this clinically important problem will give his experience.

Dr. William L. Bradford, Rochester, N. Y.: The reading of this fine paper is justified, in part, by the importance of the infections this organism causes in early life. I'm sure the combined activities of the Staphylococcus and of Escherichia coli will prevent the interest of those concerned with infections of infancy from becoming entirely viral for some time!

Dr. Hardyment's charts clearly show the current problems of resistance of the Staphylococcus to antibiotic therapy. Perhaps this fact should remind us not to forget what we know about the immunological attributes of the organism. We know a great deal about antitoxic immunity (much of which came from Canada) and less about antibacterial immunity. Very little is known about the role of nonspecific immunity in staphylococcal infections. A review of these factors might be indicated in view of the current status of this type of neonatal infection.

DR. HORACE L. HODES, New York: I should like to make one or two comments.

One point which ought to be brought out (which Dr. Hardyment told me privately) is that infants in their hospital are kept in the nursery for about a week, so that the absolute rates may be different from some of the American hospitals, in which the infants are kept in the hospital a shorter period of time.

I think another very important observation has to do with the absence of staphylococci from the nurses' hands, while the spread of infection rate appeared to go on quite unchanged. We are used to thinking, as a result of Hamburger's work, that transmission of streptococci from nose to hands is an important factor in the spread of these organisms. Dr. Hardyment's paper would seem to indicate that for the Staphylococcus, this is not the case. We are left, then, with the possibility that infection goes on with these resistant staphylococci by a transfer of droplets from the nurse to the infant.

I should like to ask Dr. Hardyment to comment on the actual numbers of staphylococci per liter of air which he found. I think this is an important point, because we have never been able, with staphylococci, to evaluate properly the importance of infection by way of the air from a remote source, as compared with that caused by the close contact. In this connection, his figures showing the number of staphylococci per liter of air would be of interest.

DR. FREDERICK W. BARNES JR., Baltimore: Today we realize that the factors of resistance may be even more important in some cases than the causative agents in the disease. It seems to me that there are interesting factors of resistance which may be of great importance in this problem. I wonder if the authors have studied any of these, such as infant gamma globulin levels, method of cleaning the skin (it is probable, for example, that scrubbing the skin or removing the corneal layer affects its resistance), pH of the skin, level of the mother's gamma globulin, nutritional status of the children and the mother, level of serum proteins and liver function, maturity of the baby relative to its degree of resistance, adrenal activity, and hormonal concentrations in blood and urine.

I should be interested to know whether Dr. Hardyment and his collaborators have had an opportunity to investigate any of these factors.

DR. HATTIE E. ALEXANDER, New York: I wonder if our Chairman, in selecting the papers, really meant this one to be included in the viral diseases. I believe he did on the suspicion that Staphylococcus may not be the primary agent in vesicular skin lesions. This also prompts me to ask whether Dr. Hardyment is really describing the results of cultures of vesicle fluid from impetigo.

A few years ago, at the Babies' Hospital (or rather in the Sloan Nurseries, supervised by the staff at the Babies' Hospital), a small flare-up of what we termed impetigo was encountered, which led us to take cultures from many babies' nasopharynx and skin in various areas to determine whether pathogenic Staphylococcus was present. Most of this work was carried on after this small flare-up occurred and in a nursery in which there was no impetigo and no clinical skin infection of any variety.

It was interesting that in over 50% of the babies, in the nasopharynx as well as on the skin, pathogenic staphylococci were cultured, even though there was no disease.

DR. LEWIS W. WANNAMAKER, Minneapolis: I should like to comment on one point. One should not assume that, because a viable organism is found in the environment, this organism is necessarily infectious.

This has been assumed for the hemolytic Streptococcus for a number of years, and many unsuccessful attempts have been made to reduce the incidence of streptococcal infections by reducing the numbers of streptococci in the environment. The failure of these attempts is not surprising. Our recent studies in military populations indicate that individuals exposed to environments grossly contaminated with viable Group A streptococci have no increased risk of acquiring acute streptococcal tonsillitis.

DR. A. F. HARDYMENT, Vancouver, B. C., Canada: May I thank all of those taking part in the discussion for their stimulating questions.

Both Dr. Clement Smith and Dr. Hattie Alexander asked if we were culturing organisms which, I understood them to imply, often reside on the normal skin and really are not from lesions. I thought that point was made clear from Slide 1. The left-hand group of figures showed that normal babies were carriers at the rate shown (21%), whereas babies with pyoderma were carriers at a much higher rate (81%).

Can it be argued that every time we grew staphylococci from a lesion, we were fortuitously encountering the 20%-30% of individuals who carry staphylococci on their skin and not the 70%-80% who were not carrying staphylococci? Inasmuch as we have recovered the Staphylococcus pyogenes from almost 100% of lesions, we feel that we were, in fact, culturing a staphylococcal lesion.

Dr. Smith has, of course, pointed out the difficulty which we mentioned in our preamble, that is, the impossibility of comparing data from different institutions. One person's idea of what constitutes a staphylococcal infection of the skin of the newborn may differ greatly from another observer's opinion. I have repeatedly encountered difficulty in discussing our data with other people. Lesions which are thought to be innocent in one nursery are viewed with horror in another. We were hoping that this study would in some way lend support to the viewers with horror.

Slide 2 showed the age of the babies in days and the number of cases found according to the age of the baby. It supported Dr. Hodes' remark that most of our cases developed between the fourth and sixth days of life. From then on, the babies are gradually being discharged. These figures do give some indication that the longer the baby is in the nursery the more likely he is to have pyoderma.

In regard to Dr. Bradford's comment, it reminds me that we have made one study about the possibility of the development of resistance of this organism to hexachlorophene. Just before I left the city, Dr. Cockcroft had submitted pyogenic staphylococci to solutions of hexachlorophene, one part to a million and, up to that dilution, they were completely inhibited.

Dr. Barnes, I am sorry that we have no evidence along the lines you suggest, in fact, those are the lines along which we propose to continue our investigations.

The last speaker, I think, was Dr. Wannamaker. He has raised the question as to whether the staphylococci are really the offenders, and, of course, we do not know that. We have considered the idea that the infection is due to a virus and the Staphylococcus is a secondary invader, but we only have bacteriological evidence.

The Pattern of an Epidemic of Infantile Diarrhea as Determined by the Tracer Organism, Escherichia Coli, 0127: B$_8$. DR. CYRIL S. STULBERG and DR. WOLF W. ZUELZER, Detroit.

A number of distinct serologic types of Escherichia coli have now been shown to be responsible for institutional outbreaks as well as sporadic cases of diarrhea in newborn and young infants. Bacteriologic, epidemiologic, and clinical data will be presented on an extensive nursery epidemic caused by a newly described pathogen, E. coli 0127: B$_8$. The epidemic, which involved a total of 60 cases over a period of four months, was characterized by a cyclic series of flare-ups.

Because stool specimens, daily cultures of the predominant organisms, and acute and convalescent sera were systematically saved from each infant until the identity of the etiologic agent could be established, it became possible, with a specific antiserum, to make a complete study of the epidemic, using this organism as an etiologic tracer.

The bacteriologic basis for the cyclic pattern of the epidemic then became apparent. Each cycle began with a build-up period during which cross infections and incubation stages were occurring. The incidence of diarrhea increased slowly at first and then rose sharply to a peak. Each sick infant exhibited virtually pure cultures of E. coli 0127: B$_8$ in its stools. Treatment of the sick infants with neomycin resulted in prompt individual improvement and in a sharp decline of the outbreak which coincided with the disappearance of E. coli 0127: B$_8$ from the stools. With the cessation of the antibiotic a new cycle began. There was an almost immediate resurgence of the pathogenic organisms in the stools, resulting invariably in asymptomatic carriers, a few clinical relapses, and an increase in new diarrhea cases.

Control of the epidemic was not accomplished until all infants, whether they had diarrhea or not, were simultaneously placed on neomycin therapy, thus eliminating the organisms from the nursery.

The implications of these findings in the recognition and control of nursery epidemics of infantile diarrhea will be discussed.

DISCUSSION

DR. WOLF W. ZUELZER, Detroit: I want to make only one brief addition to the data which Dr. Stulberg has presented. We became interested, of course, in the same sort of problem which the previous speaker discussed in relation to Staphylococcus, the method of introduction of the organism into the nursery.

We were unable to demonstrate the source in the nursery personnel, but we did find, during the last period, (Phase 5 in those slides of Dr. Stulberg's) that two infants were admitted from the outside with positive cultures. Ours is not a nursery in the sense of a newborn nursery attached to a hospital obstetrical unit; the infants are brought in from the outside.

These two infants, during the period of observation represented here, were admitted as apparently healthy newborn infants, one from a nursery where no epidemic was present and the other from a home. Without our ability at that point to serotype, we would have had a perfectly ideal source for an epidemic, assuming that this organism represents the etiological agent.

We are very much concerned, of course, with the question as to whether here, again, we merely have an organism which traces the epidemic out for us and is somehow associated with a virus; those studies are now in progress. But, as of now, with the results of neomycin therapy confirming it, we have (to our satisfaction, at least) concluded that the 0127: B$_8$ is indeed an etiologic agent of infantile diarrhea.

DR. STEWART H. CLIFFORD, Brookline, Mass.: I was disturbed last year by Dr. Warren Wheeler's presentation of a similar epidemic and am further worried by this presentation, for both imply the failure of present techniques to control the spread of this type of enteric infection.

All of us in charge of newborn services of the type which Dr. Zuelzer has just described, where we admit babies from the outside, have a real stake in this problem. Fortunately, thus far, we have not encountered this type of pathogenic E. coli epidemic, and only rarely have we been able to identify pathogenic colon bacilli in individual infants with diarrhea.

DR. HORACE HODES, New York: I should like to make one or two remarks about this interesting paper. I should like to point out one interesting fact which time did not permit the author to emphasize. That is, that infants do not have anti-E-coli antibody transferred by way of the placenta from the mother. This fulfills one theoretical necessity for the importance of E. coli, since the newborn infant is not protected by the mother's antibody.

I should say, too, that Adamson studied 115 mothers showing bacterial antibodies against various types of coli, and found that practically none of their newborn infants had such antibodies.

I should also like to emphasize the importance of the coli by pointing out that, normally, groups of individuals do not possess the same E. coli strains and therefore could not transfer a single type of colon bacillus to all those about them. It would be extremely unusual, in normal circumstances, to have a particular, single type become the dominant organism in a great number of adults. The same thing, we think, is true in the newborn infants. In the last year. we have studied infants as they were born in the nursery. No such pattern as was shown by Dr. Stulberg has been encountered; in fact, we have not encountered any of the recognized strains of pathogenic colon bacilli.

I should like also to ask Dr. Stulberg a question. He did not have time to discuss the type of antibodies which he studied. I should like to know whether it was anti-O or anti-B antibody which he demonstrated by Dr. Wheeler's technique. I think it might be more important, perhaps, if it were anti-B, because all colon bacillus strains which are believed to be capable of causing diarrhea possess B antigens.

DR. ERWIN NETER, Buffalo: I think that Dr. Stulberg has made a very important contribution to our understanding of the apparently numerous etiological agents responsible for epidemic diarrhea of infants, and it is only appropriate, before this gathering, to call attention to the fact that it was the British investigators who led the way, 10 years ago, through their studies from 1945 on—Dr. Brey, Dr. Joan Taylor, Dr .Keith Rodgers, and others.

So far as the hemagglutination test is concerned, I am delighted to learn that the results of Dr. Stulberg are in entire agreement with ours. We have just completed the study of 320-odd

serum samples of children of various ages, and we found—and this is rather interesting—that in infancy the percentage of sera containing hemagglutinins against these E. coli strains is extremely low and that the percentage of positive sera increases with age. Interestingly, too, it reaches over 95% in adults.

Examining some 27 cord sera parallel with the maternal sera, we found that, in the vast majority of serum specimens, the mother's serum contained these antibodies and the cord serum did not. In the few instances where antibodies were transferred, the titers in the maternal sera were from fourfold to sixteenfold higher.

In the evaluation of the role of these E. coli strains, it is worth while to point out that these serogroups are not the ones which are associated with other E. coli infections, such as pyelitis and peritonitis, and it is for this reason I suggested the term "enteropathogenic E. coli."

In this connection, I believe the observation by Dr. Ferguson, from Michigan, is very significant, namely, that the feeding of two of the serogroups (111 and 55) to adult human volunteers resulted not only in the development of diarrhea, but also in a demonstrable antibody increase. It is significant, also, that the feeding of a normal strain of E. coli obtained from a normal, healthy infant did not cause diarrhea, nor did the volunteers, as determined in a cooperative study with the hemoglutination method, develop antibodies to that normal strain.

All the data suggest that these special types of E. coli, indeed, are the cause of the disease.

Dr. Merlin L. Cooper, Cincinnati: I should like to emphasize two points in connection with this type of study.

First, we studied a similar epidemic in the latter part of 1953 and not only developed a wholesome respect for the capabilities of the specific serotypes of E. coli but learned that a number of our babies were also harboring the E. coli 0127: B_8 in their throats. I think this is extremely important information, since ordinarily in handling patients with diarrhea we are more prone to think, teach, and emphasize that it is only the intestinal contents which contain the etiologic agent and overlook the possibility, as it exists in these patients, of transmission of the etiologic agent from another source.

Second, in order to obtain information regarding the incidence of the presence of the specific serotypes of E. coli in babies with diarrhea, we have instituted a procedure, since our epidemic, whereby rectal swab cultures are obtained on all babies admitted to our infant wards regardless of the presence of diarrhea. The results have been illuminating, since, during the past 14 months, we have isolated from 87 patients with diarrhea 87 strains of the 9 serotypes of E. coli considered by Dr. W. H. Ewing to be associated with outbreaks of epidemic diarrhea among infants.

During the same 14-month period we have isolated Shigella from 62 patients and Salmonella from 51 patients. These findings would seem to indicate that the incidence of diarrhea associated with the presence of specific serotypes of E. coli was greater than was the incidence of diarrhea associated with either Shigella or Salmonella.

Dr. Cyril S. Stulberg, Detroit: I should like to thank the discussants for their comments.

In answer to Dr. Clifford's questions, I believe our nursery followed the generally accepted rules. However, you must realize that these infants came into the nursery without symptoms of diarrhea yet carrying pathogenic coli in their stools. One can easily see how these carriers, excreting large numbers of organisms, transmit the pathogens from one infant to another.

While the infants were in the incubating stage of the disease, of course, the infection was not recognized. Nevertheless, as soon as a few cases were recognized, such infants were isolated, using the block system. When one does encounter an epidemic of this nature, however, it is often so explosive that obviously the nursery would have to be closed if methods were not available for recognizing the organisms and controlling the disease.

In answer to Dr. Hodes' question we suspect that the antibodies we are measuring are predominantly against the B antigen, for the following reasons. Red cells are sensitized by adsorbing antigen for one minute. They are then tested separately with rabbit antisera containing only the O antibodies and antisera which have both the O and B antibodies. The OB sera produces a maximal hemagglutination titer, whereas the O sera exhibits a low titer. However, if the red cells are allowed to adsorb antigen for one-half hour, the titer of the O antiserum approaches that of the OB serum. This would suggest that the B antigen is adsorbed more rapidly and with cells sensitized for one minute the antibody being measured in the human serum is predominantly B antibody.

I am sorry that time does not permit me to comment further on points of discussion.

Induced Heritable Change in Poliomyelitis Viruses. Dr. Katherine Sprunt, Dr. Isabel Morgan Mountain, Winnifred R. Redman, and Dr. Hattie E. Alexander, New York.

A number of poliomyelitis virus strains have been described recently which after growth in certain selective environments show heritable changes, such as loss of virulence or ability to multiply in unusual hosts. This approach to the genetic study of poliomyelitis viruses utilizes selection according to their different growth requirements of the spontaneously occurring mutants which appear naturally in these as in any large populations of micro-organisms. Induction of heritable changes, if feasible, rather than selection of spontaeously occurring mutants would seem to offer a more efficient approach to the search for poliomyelitis viruses with desired combinations of heritable traits.

Several different methods have induced heritable changes in bacteria and bacterial viruses, changes probably brought about by interaction of the nucleic acids of two genetically different organisms. "Recombination" of genetic traits in the progeny following growth together in the same host cell of two different but related parent viruses has been reported for bacterial viruses and influenza viruses. This principle has been used in the experiments to be reported.

Type I and Type II strains of poliomyelitis virus were grown together in monkey-kidney-cell cultures in such proportions that infection of most of the cells with at least one particle of each type of virus should have occurred. These circumstances will therefore probably provide an opportunity for interaction of the genetic material of the two types. The progeny from viruses grown together in such a manner have been compared with progeny of control mixtures of the two types of virus, in which no opportunity has occurred for intermingling of genetic material. The data show that a large proporition of the progeny of one experimental population can be neutralized by Type I as well as by Type II antiserum, suggesting that antigenic traits of Type I and Type II viruses have apparently been combined within the same infectious particle. These results were regularly reproducible and were significantly different from those obtained from control mixtures.

The new doubly neutralizable combined form of virus was demonstrable after seven passages, five of which were from limiting dilutions. The new form appears to reproduce as such, but it is demonstrable in only approximately half of the progeny studied from limiting dilutions as the major component of the virus population. Experiments designed to obtain a combined form which is stable and free from parent virus are in progress. The possible nature and significance of this combination form of virus will be briefly discussed.

DISCUSSION

Dr. Hattie E. Alexander, New York: Our primary interest in these results is the suggestion that the principles found to govern the heritable traits of a number of other micro-organisms may apply to polio viruses. All the heritable changes which have been induced in micro-organisms would seem to result from the interaction of the nucleic acids of two related but genotypically different organisms.

Three methods have been used for providing an opportunity for this interaction.

1. *Transformation.*—This process represents the transfer of a single new genetic trait to a viable recipient population of bacteria by exposure for less than five minutes to a purified or crude deoxyribonucleic acid (DNA) extract from the donor cell. There is convincing evidence that the dynamic component of the gene or heredity determinant is the DNA itself, in pneumococci, Hemophilus influenzae, and meningococci.

2. *Transduction.*—The transduction phenomenon is similar to transformation in that only a single new genetic trait is induced in bacteria at a time; the change follows the invasion of a bacterium by a bacterial virus which introduces genetic material from a previous host. Induction of virulence in nonvirulent diphtheria is probably an example.

3. *Recombination.*—While certain heritable changes induced in bacteria represent recombination, this method has been used primarily for the change in heritable traits of viruses and occurs when two appropriate viruses multiply in the same cell. The result is a reshuffling of the parental genes in the progeny, producing new combinations of genetic traits.

A. *Bacterial Viruses.*—All evidence indicates that recombination in bacterial viruses results from the interaction of the DNA's of the two viruses. The occurrence of recombination is well established for bacterial viruses and permits interpretation of variation and evolution along more or less classic genetic lines.

B. *Influenza Virus.*—Hirst and associates and Burnett and his group have induced heritable changes in influenza viruses following growth of two different variants of influenza A in the same cells. The new influenza viruses produced by Hirst and Burnett combined the antigens of both types within the same particle and also exhibited evidence of interchange of other genetically different traits of the parent viruses.

C. *Poliomyelitis Combined Particle.*—The combined poliomyelitis virus just described might also represent a genetic change which resulted in a combination of antigens of two types within the same particle and in addition suggests an interchange of the heat-susceptibility trait or reshuffling of the parent traits. To establish this point, it will be necessary to reproduce these results, using parent viral populations derived from single particles. The Dulbecco technique is being used for this purpose.

A poliomyelitis particle combining Type I and II antigens will be of interest to those who believe in the oral use of attenuated live virus for immunization. The use of two types of poliomyelitis viruses simultaneously for this purpose has yielded results which suggest interference between the two. The combined virus might solve this problem.

The Inactivation of Newcastle Disease Virus by the Properdin System. Dr. R. J. Wedgwood, Dr. H. S. Ginsberg, Dr. R. H. Seibert, and Dr. L. Pillemer, Cleveland.

Pillemer and his colleagues have recently described a protein found in normal sera, designated properdin, which in conjunction with complement and Mg^{++} destroys or inactivates such diverse agents as bacteria, foreign or abnormal red cells, and, as shown below, viruses in the absence of specific antibody.

Ginsberg and Horsfall demonstrated a heat-labile factor in serum that inhibited both the in vivo and in vitro action of certain viruses. Their studies indicated that hemolytic complement was not alone responsible for the antiviral action of serum. The role of properdin in such virus inactivation was, therefore, investigated, and the results of these studies form the basis of this report.

Newcastle disease virus was employed as the test agent because specific antibodies are not found in human sera. Viral activity was measured both by hemagglutination of chicken red cells and by infection of chick embryos. Under controlled conditions, removal of properdin from serum by adsorption with Zymosan at 17 C, without significant reduction in the components of complement, rendered the serum unable to neutralize virus. Addition of purified properdin restored antiviral activity. By varying the quantity of purified properdin added to sera from which this protein had previously been absorbed, it was shown that a very small quantity was essential for neutralization of virus and that an excess of properdin did not increase antiviral activity. The data obtained indicate that properdin, all components of complement, and probably divalent cations were necessary for fresh serum to manifest its heat-labile antiviral effect.

Conclusions.—The heat-labile antiviral activity of fresh serum can be removed by the removal of properdin from serum and can be restored by the readdition of purified properdin. Removal of any component of complement from serum also inactivates the viral inhibitory effect. It is apparent that the properdin-complement system, which is present in normal sera, has potent antiviral as well as antibacterial activity.

DISCUSSION

Dr. Joseph Dancis, New York: Some years ago we were interested in the bacteriostatic effect of human serum against Escherichia coli. We used as our test organism E. Coli 055, supplied to us by Dr. Hodes.

We were very much puzzled by what we found. The serum of cord blood inhibited the growth of the organism very effectively; this property tended to disappear from the serum toward the third month of life and reappear at the end of the first year. Its general curve followed pretty closely that of gamma globulin. The activity was destroyed by heat and could not be restored by the addition of complement. It apparently was transferred across the placenta, differing in that way from certain antibodies against E. coli reported on this morning.

We left the problem unresolved and called it by a noncommittal term used in the past, "natural antibodies." I wonder if Dr. Wedgwood's investigations have gone far enough to state whether we may have been dealing with the properdin system?

Dr. Frederick W. Barnes Jr., Baltimore: This is a very important paper, Dr. Wedgwood.

The implications of Dr. Wedgwood's work are that the properdin system consists of very few different kinds of components, perhaps only one or two. On the other hand, the inhibitory action of serum might, of course, be very complex, involving polysaccharides and many kinds of proteins and other systems. If the inactivation described by Dr. Wedgwood were caused by enough different kinds of protein molecules as well as by other systems, the implications of the findings would have different bearing on our thinking about this phenomenon than if the inactivation were caused by a highly identifiable and singular system. Since this feature of the properdin system has not yet been well defined, I wonder if Dr. Dancis and Dr. Wedgwood, who have done much work in this direction, would comment on this particular point.

DR. R. J. WEDGWOOD, Cleveland: I want to thank the discussers for their kind comments.

We looked at Dr. Dancis' paper with a great deal of interest when it came out. I do not think we have answered the question I am asked, that is, "Does properdin exist, and does it disappear and then reappear later?" We have found it in cord blood. We are trying to follow it over a long period of years.

I do not know quite how to answer Dr. Barnes' question. I am sure there must be substances other than properdin which have natural resistance mechanisms, but, to date, the properdin seems to be remarkably clean, and all the data we have seem to indicate that in its activities against one virus and the amount of bacteria we tested exactly the same mechanism is going on. It is indeed one system with multiple assets.

A New Type of Antibody and a "New Concept" for Antibody-Antigen Interaction.
DR. VICTOR A. NAJJAR and JEAN FISHER, Baltimore.

Antisera to yeast alcohol dehydrogenase were produced in rabbits by multiple injections given subcutaneously. The antibody reacted readily with the enzyme to form a precipitate (antibody-enzyme complex) which still possessed considerable enzymatic activity. The antibody did not react with liver alcohol dehydrogenase. A study of the kinetics of the precipitin reaction at 0 C showed a fast rate followed by a much slower one proceeding in a linear manner with time. This indicated the presence of two distinct types of antibodies.

When antibody was added to a constant amount of antigen (enzyme) a point was reached where all the antigen (enzyme) was precipitated by a definite amount of antiserum. Further additions of antiserum, however, resulted in further precipitation of antibody and further inhibition of the enzymatic activity of the complex. This occurred even when antiserum additions were made after the supernatant had already contained many times the amount of antibody necessary to precipitate the enzyme. These observations led to the hypothesis that the two types of antibodies present were antibodies of the antigen (enzyme) and antibodies to the complex. Injection of the complex resulted in antiserum which reacted with the complex faster than it did with the enzyme as measured by rate of turbidity formation and rate of inhibition of enzymatic activity.

It was possible to absorb the antibodies to the complex by exhaustive addition of the antigen-antibody complex until no further reaction occurred. Following this, the addition of the (enzyme) antigen resulted in immediate precipitation of antibody. At the equivalence point there were 4 molecules of antibody combined with 1 molecule of antigen and in antibody excess there were 12 molecules of antibody combined with 1 molecule of antigen.

After one injection of antigen about 0-70γ of antibody to the complex was formed per milliliter of serum. Antibody to the antigen amounted to about 100-200γ per milliliter. Following the second injection, 500-1000γ per milliliter of antibody to the complex was formed and 700-800γ per milliliter against the antigen.

The occurrence of an antibody to the antibody-antigen complex serves to explain a lot of the mysteries of antibody-antigen interactions:

(*a*) Incomplete univalent antibodies that precipitate in the presence of the multivalent antibody are, in fact, antibodies to the complex.

(*b*) The mere existence of the so-called equivalence zone and its increase in magnitude with successive courses of immunization is now understandable.

(*c*) The deposition on the antigen of more antibody molecules than one antigen molecule can hold is no longer a mystery.

Certain allergic phenomena, such as (*a*) the occurrence of two bouts of serum sickness after one injection of serum, (*b*) the reappearance of glandular swelling in scarlet fever after cure,

and (*c*) the reappearance of redness and swelling at the site of an already healed smallpox vaccination can now be explained by interaction of antibody to the complex with the complex formed.

DISCUSSION

DR. FREDERICK W. BARNES JR., Baltimore: I have one question to ask. Since antibody response is now known to be complex in the first place, involving a number of molecules of various kinds and showing a sort of spectrum of antibody response in serum, I wonder if most of the observations in the phenomena observed by Dr. Najjar could not fall under another explanation. It seems to me that the various degrees of antibody interaction which he finds could be easily explained by the presence of several kinds of antibodies to the antigen. Some of these antibodies might have specificity directed more highly to one group of sites on the antigen molecule, others to another group. Some of the sites might involve enzyme activity and some might not. Some of the antibodies might have a high degree of specificity, some might have a lower degree of specificity. Some might not give precipitins until a lot of preliminary agglomeration and polymerization had taken place between antigen and antibody molecules. It seems to me that these standard explanations must be considered as a way of thinking about this particular phenomenon. I wonder if Dr. Najjar would care to discuss this.

DR. WALTER HEYMANN, Cleveland: This paper is most stimulating indeed.

A few years ago we found that the injection of antikidney serum produces a nephrotic type of kidney disease. We also found that a metabolic lesion was produced in the renal cortex, in that the utilization of glucose and fructose became abnormal.

Now that Dr. Najjar has worked with an enzyme active as an antigen, I can well understand how an antibody-antigen reaction may lead to a cellular metabolic lesion.

Avian antikidney sera give rise to a latent period which is not noted when nephrotoxic sera are obtained from rabbits. The pathogenesis of this latent period is not fully understood. I should like to ask Dr. Najjar whether he believes that the mechanism of antibody formation to antigen-antibody complex may be at play and could explain this phenomenon.

DR. LYTT J. GARDNER, Syracuse, N. Y.: I should like to suggest that Dr. Najjar's concept has application to the protein growth which occurs in normal embryologic development. If we recall the experiments of Spemann and the role of organizers in embryologic growth, it might be fun to think of the original antigen as an organizer. The new protein generated by the organizer would be "antibody." Thus we would have an organizer-protein complex which, in turn, stimulates further recombinations, after the manner described by Dr. Najjar for his antibody-antigen interaction.

It would be quite provocative to explore this in connection with normal protein growth. It might well be that we could paraphrase an old axiom and say that ontogeny recapitulates this concept which we discuss today.

DR. ROBERT SLATER, New York: There are a couple of questions I should like to ask Dr. Najjar in order to clarify my thinking.

Am I correct, Dr. Najjar, in interpreting that the combination of antigen plus antibody becomes a complex which is then further antigenic within the same animal as a complex, and that the animal goes on to produce antibody directed against his own gamma globulin within the complex, and that this sequence of events is repetitive producing increasing size and modification of the antigenic complex as homologous antibody is sequentially added?

I am interested in this consideration, since gamma globulins, as a family of proteins, are quite similar immunochemically. Do you think that the considerable differences in precipitating capacity which you have shown could be accounted for by modification of the gamma globulins as complexed proteins, in view of their close "native" cross reactivity.

The other point I should like to question relates to the combination of antibody or gamma globulin to definite sites on the enzyme antigen and the role of this enzyme-gamma-globulin complex as a modified antigen within the animal which you proposed. Could the changes in the specificity of the precipitating system with time be an expression of progressively broad antibody formation directed toward a number of surface or polar groups in the original enzyme antitgen?

DR. ALLAN M. BUTLER, Boston: I am sure that Dr. Najjar is very familiar with the work of Dr. Linus Pauling bearing on the ideas just expressed by Dr. Gardner regarding the physicochemical determinants of the production of specific protein molecules. I wonder if he thinks it appropriate to give us the benefit of elaborating on that a bit.

DR. VICTOR A. NAJJAR, Baltimore: Upon thinking earlier about my talk and of how I could end it wittily, I decided to include among my remarks, as I thought I could, a comparison to Arrhenius, while asking the audience to forgive the comparison between Arrhenius and myself. However, I forgot to beg forgiveness. May I now be forgiven for my forgetfulness.

With reference to the questions, I must ask for a good measure of forbearance from those who asked questions, because I am afraid I have not kept them all in mind. If I omit any answers, it should not be construed as a means of ducking sniper's bullets.

Dr. Barnes asked if the antibody that reacts with the complex is merely a different antibody naturally precipitating on an exposed antigenic surface.

This is not the case for this one simple reason. If you have an antibody-antigen complex you have an antibody which covers Site A and leaves Site B open, then in another an antibody which covers Site B and leaves Site A open, and if you should use this complex for the purpose of absorbing excess antibody to A and in B sites, then you should absorb all the antibodies and not leave any behind, because, statistically, enough Surface A and Surface B would be available in the elements of the complex to absorb all the antibodies available. On the contrary, we leave a lot of antibody behind in the supernatant when we absorb with one complex.

Dr. Gardner's suggestion is a very good one for the simple reason that we have given it quite a bit of thought. Dr. Lytt Gardner and Dr. John Cobb independently suggested to me the idea that growth of tissue may involve principles similar to those I have cited for antibody-antigen interaction.

As to Dr. Slater's questions, I do not think I shall be able to answer all of them, because some of them were asked while I was writing the previous ones.

One of the questions was whether the complex which is formed is directed against the gamma globulin and whether this may explain the growing system of the gamma globulin.

In the slide I intentionally attached the antibody both to the antigen and to the antibody portion of the complex. The antigen we used has a molecular weight of around 150,000, and the rabbit antibody has a molecular weight around 180,000. I was rather generous and depicted them as similar in size. In doing so I was trying to take a disadvantage. On the basis of their being similar in size, one should be able to put 16 molecules of antibodies on 1 molecule of antigen, if at every random area there would be a site available for an antibody. This is in fact a real impossibility.

We have been able to place 12 molecules of antibody on one molecule of antigen with no attempt at attaining maximal reactivity. This number, which is not even a maximum ,is larger than would theoretically be possible. Therefore, some of the antibodies must sit somewhere, and they must be directed against the antibody portion of the complex. On that basis, it is conceivable that this latter antibody would have an affinity to the natural (nonantibody) gamma globulin, giving rise to a growing system of gamma globulin. This might explain the case by which gamma globulin can be disrupted.

This suggestion does not call on new principles; it clearly fits within the realm of biochemistry and protein chemistry as we know them today.

A protein is in a certain state which is defined by its environment, and as soon as we alter the environment we alter the physical configuration of the protein simultaneously.

It has been shown that when two proteins interact, both of them are simultaneously modified; not only is their shape modified, but also the volumes of the molecules increase.

Some time ago, Campbell and Johnson in California studied the change in volume of the antibody against the pneumococcus polysaccharide after union with the antigens. They found that the antibody increased in volume by 50 cc., which is considerable. In other words, those antibodies have changed in configuration and have thrown out certain groups which made them occupy more volume and more space in water.

One may therefore assume that these new groups are now antigenic and exposed to the body mechanisms which form antibodies; the resulting antibodies are now directed against the modified normal globulin.

This is not a new principle. It has been shown repeatedly that you can add alum (or, for that matter, tubercle bacilli) to hitherto nonantigenic proteins and render them antigenic and produce antibodies against them.

So it is my firm belief that, sooner or later, somebody (if we do not) will finally prove the interaction of antibody with another antibody of the same species. We hope to be able to do that. I am afraid that is all I can say on this subject.

With reference to Dr. Butler's question, I think it was generous of him to ask me to elaborate on how antibodies are formed. I probably will not have very much time.

I can tell you this, though. If I were to elaborate on how antibodies are formed, what their purpose is, I would strongly imply that antibodies are merely carrier proteins that are constantly being formed adaptively to carry serum constituents which are not water soluble. When such proteins are elaborated in adaptation to a lipid for the purpose of transporting it to and from tissues, we call them lipoproteins. On the other hand, when formed in response to a foreign protein, we call them antibody protein. In the former instance, the lipid is rendered available to the cellular elements of metabolism, and in the latter, the toxin is made accessible to the cellular elements of immunity. Some of these carrier proteins have surface configurations that happen to be complimentary to a common surface structure in bacteria.

For instance, starch and glycogen, cellulose and other polysaccharides have common configurations; so a protein which is formed with a complementary surface against this common configuration is quite apt to combine with any of these particular polysaccharides. The properdin system would fit into this category.

I probably should not elaborate any further, because you may not wish to be indentified as having had the patience and tolerance to listen to these unorthodox ideas.

Viremia in Primary Smallpox Vaccination and Its Complications. Dr. C. Henry Kempe, San Francisco.

For many years past our concept of the pathogenesis of smallpox vaccination has included the thought that vaccinia virus enters into the bloodstream at some time after primary vaccination and can be demonstrated in the blood and also, on occasion, in the nasopharynx and spinal fluid.

An extremely sensitive tool for the isolation of vaccinia virus has been developed, utilizing the chorioallantois of the fertile hen's egg. Systematic search to determine the presence of vaccinia virus in the blood of 100 children vaccinated by the routine method has failed to result in virus isolation in even a single instance, regardless of what period in the course of primary vaccinia the virus isolation was attempted.

Failure to isolate vaccinia virus from the blood in the course of vaccinia contrasts sharply with the situation found in children who are suffering from serious complications of smallpox vaccination, including generalized vaccinia, eczema vaccinatum, and vaccinia necrosum.

Clinical and laboratory evidence will be presented to show that viremia probably occurs regularly in these conditions and that faulty immune mechanisms are responsible for the development of these serious complications.

Further Clinical Observations in Galactosemia: A Possible Mode of Production. Dr. George Komrower, Manchester, England.

The finding of a marked aminoaciduria in untreated cases of galactosemia has been repeated in two other children; this was associated with a marked proteinuria. In all children both conditions returned to normal when a lactose- or galactose-free diet was introduced. These conditions have been reproduced in one child now aged 3 years. Evidence is presented to support a renal aminoaciduria.

A marked acidosis has been demonstrated in two infants on galactose or milk diets; this also disappeared when the special diet was recommended. Investigations suggest that this is a renal acidosis similar to that found in hyperchloremic acidosis and that the condition becomes increasingly difficult to reproduce as the infant develops.

It is thought that these findings are due to the presence of a toxic agent in the cells and, from the work carried out, that this substance is galactose-1-phosphate.

DISCUSSION

Dr. Samuel P. Bessman, Baltimore: The data here seem to show two things: one that Dr. Komrower did not emphasize, I believe, is that in galactosaemia there is also an increase in the glucose phosphate. The glucose phosphate appeared to be, at least on the charts, a little higher than the glucose phosphate in the normal children.

The question one can raise is that, although galactowaldenase is possibly lacking in these patients, and there is an accumulation of galactose-1-phosphate, as has been shown, what

deleterious effect does the collection of galactose-1-phosphate have in the first place? In other words, how does this accumulation (which we will say does exist) have a particular bearing on the metabolism of the cell?

DR. FREDERICK W. BARNES JR., Baltimore: This is a very beautiful paper, and I wish to congratulate Dr. Komrower on such a clear-cut result and a definite advance in this field.

One interesting observation which has been made lately on several enzyme systems, which I think bears on this very critical problem of whether galactose-1-phosphate is a toxic material, is the fact that several enzyme systems operating in a cell have been shown to be greatly slowed down in activity, greatly inhibited, by normal substrates.

In other words, if an enzyme ordinarily operates on two or three substrates (say, a two-substrate system), to give products and perhaps equilibrium, and if we have, therefore, as many as four substrates which it can act on, any one of those can inhibit the activities of that enzyme toward any or all of the others.

Therefore I think that, if galactose-1-phosphate is a normal step in cellular metabolism, the build-up of galactose-1-phosphate might indeed operate in the above fashion without calling in, as an explanation, the possibility of its being and unusual toxic phenomenon.

I do think that I would be interested in the evidence for the plasma amino acid not being elevated. The estimation of plasma amino acid is difficult to make quantitatively; the normal variation is considerable, and several instances of amino-aciduria, earlier expressed, have had to be somewhat revised as to explanation, because it has been found that there is some elevation of plasma amino acid.

I think also that the more amino-aciduria is looked for in normal persons, the more is found. For example, during the summer months, a number of normal people have been found to spill amino acids in the urine.

DR. RICHARD WAGNER, Boston: I have two questions to ask Dr. Komrower:

(1) Was the method of Hanes and Isherwood used for the chromatographic identification of galactose-1-phosphate, and was the solvent butanol-picric acid?

(2) If galactose-1-phosphate is present in the red blood cells of the patient, easily hydrolyzable phosphorus should be demonstrable. I wonder if this technique was applied.

DR. GEORGE M. KOMROWER, Manchester, England: To answer Dr. Bessman, I think possibly it is my fault for not making this clearer. We are not considering galactose-1-phosphate itself as a toxic agent. We are suggesting that there is an interference with cell metabolism shown by the figures for the oxygen take-up. The increase in the amount of galactose-1-phosphate may mean a reduction in the amount of glucose available in the cell and so diminish the amount of energy available for the cell metabolism.

I do not think we have any evidence at all to suggest that the substance in itself is a toxic agent.

Dr. Barnes, we thought that this was possibly an expression of competitive inhibition, but we did not know exactly what other enzyme system was being inhibited.

As far as the plasma amino-nitrogen levels are concerned we used the ninhydrin method in this particular instance. To answer Dr. Wagner, the method for the isolation and chromatography of phosphate esters he suggested was carried out using deproteinized, hemolyzed blood. We did notice in our phosphate estimations that the total amount of ester phosphate is reduced during the course of milk feeding.

Tuberculous Meningitis in Children. DR. GLADYS BOYD, Toronto, Canada.

The observations in this paper are based on the study of 140 treated cases of this disease admitted to the wards of the Hospital for Sick Children, Toronto, between December, 1946, and March, 1955. It includes 15 patients without bacteriological proof of the disease in their spinal fluids. Twelve others were admitted to hospital during this period, but are not included as they died within 24 hours of admission.

The chief aspects of the disease to be discussed are types of disease, treatment, including prophylactic therapy and those measures directed towards helping the host, as well as the chemotherapeutic ones. The morbidity and mortality under the regimens used to reduce the mortality from almost 100% to a low level will be considered.

DISCUSSION

DR. DAVID GREELEY, Boston: How many patients developed meningitis while they were under observation?

DR. G. M. NICKERSON, Montreal, Canada: I have a slide which I should like to show in just a minute—50 patients treated quite differently from Dr. Boyd's.

This attempts to illustrate progressive elimination of mortality and sequelae at the Alexandria Hospital, in Montreal, where a ward is maintained for a childhood tuberculosis. In the left-hand column you may see duration of and significant factors in therapy, and the bottom line indicates patients who survived without sequelae. Prior to P. P. D. therapy there were no recoveries of 10 admissions. In the following year—1950-1951—eleven patients were admitted with tuberculous meningitis, only two of whom died, both accidentally.

Only two factors of therapy had been changed—namely, the duration, from three months to seven months, and the administration of PPD. Seven of these children were deaf, and it was reasoned that this was related to the amount of intrathecal streptomycin (50 mg.).

The second year the dosage of intrathecal streptomycin was reduced to 25 mg. (daily for 40 days and thereafter every second day until 200 days), and, as you may see, there has been no deafness since that time.

The third year 15 patients were admitted, with 11 survivals. Orthopedic deformities were eliminated by adequate physiotherapy. Eight children experienced recovery without sequelae, the other three having varying degrees of intellectual impairment.

In the final year, until November, 1954, fourteen patients were admitted and all survived, one infant having mild intellectual sequelae, but now appearing to be developing surprisingly well.

All cases are included which came over the threshhold—all but one were proved bacteriologically by culture. As you may see, four patients were considered to be beyond all hope at the time of admission. Five of six deaths have been attributed to inadequate control of increased intracranial pressure. Over all, there have been 10 deaths in 50 cases.

It is our opinion, and there is bacteriological support, that PPD. has been of therapeutic value: certainly no great distress has been caused by PPD. as we have used it. Furthermore, we have evidence bacteriologically that isoniazid is a definite advance in chemotherapy of tuberculous meningitis.

These children have all been followed regularly in our clinic. Electroencephalograms done since 1950 indicate that a majority exhibit some residual changes. Psychometric examinations indicate that all have normal or low-normal intelligence. Nevertheless some of the children who appear normal and who compete well at school exhibit some degree of selective brain damage.

DR. ALAN MONCRIEFF, London: I should like to congratulate Dr. Boyd on her figures and the lovely diagram she showed us; but I really got up to say that, in our country, this is a disappearing disease, and I venture the results we have heard this morning will simply become of historical interest.

The reason it is disappearing is that we have a valuable way of preventing this disease, in very stringent regulations about the periodic x-ray of all those concerned with children. All schoolteachers have to have an annual examination; all those concerned with children in nurseries or children's homes, all new residents, all nurses who come to children's hospitals.

I am quite sure that this picking up of the early, unsuspected case is a very material factor in preventing the appearance of tuberculosis in the adult, and that reflects itself in the rapid disappearance of meningitis in our country.

I think perhaps that is something we should turn our attention to. It is perhaps not entirely in our hands. The rather dramatic control of this disease in the hospital naturally attracts us; but the dull, plodding work outside, in my view, is the real answer to the problem.

DR. GLADYS L. BOYD, Toronto, Canada: In reply to Dr. Greeley, about the incidence of meningitis developing among the children with primary tuberculosis kept under observation, we believe this complication is very rare. Two children who were in the sanitarium for treatment of pulmonary disease (in 1951) developed meningitis four and six months after treatment with streptomycin. Both patients made a good recovery.

The positive reactors regularly followed in clinics have rarely succumbed to this complication. This is the factor which makes one not too hopeful about Dr. Lincoln's plan of prevention by giving these children isoniazid. The project is of great interest, and we are active participants in it.

The discontinuance of intrathecal therapy since isoniazid became available has been abundantly justified by the results in our meningeal cases.

Satisfactory levels in the spinal fluids are obtained of both streptomycin and isoniazid. The improvement in the progress of these cases with oral isoniazid and intramuscular streptomycin without use of the intrathecal route has been as dramatic as the fact that you could save a few lives with streptomycin when it first became available.

Study of Twenty-Four Cases of Ectodermosis Erosiva Pluriorificialis (Stevens-Johnson Syndrome). Dr. J. H. Charbonneau and Dr. J. L. Desrosiers, Montreal, Canada.

Twenty-four cases seen at Hôpital Pasteur from 1940 to date are briefly reviewed. Differential diagnosis is discussed together with etiological factors, complications, and prognosis. Color slides of skin and mucous alterations will be shown. Supportive treatment of shock and antibiotic prevention of secondary infections is discussed in the absence of etiological treatment.

DISCUSSION

Dr. Alfred M. Bongiovanni, Philadelphia: We have evolved a plan of treatment for these patients which is similar to that described and have been gratified with the results. In addition to proper fluid therapy and plasma infusions when indicated, we employ rather large doses of hydrocortisone. During the first 24-48 hours we continuously infused the water-soluble hemisuccinate of hydrocortisone (The Upjohn Company) at a rate approximating 2-3 mg. per kilogram of body weight per 24 hours. Thereafter we employed intramuscular hydrocortisone, about 10 mg. per kilogram every second to third day, scaling down the dose with improvement. For the latter purpose there is a concentrated preparation available, hydrocortisone acetate (The Upjohn Company), 250 mg. per milliliter. Aside from the good response noted so far, the hospital day has been shortened. We also employ antibiotics and upon occasion antihistaminics.

Dr. Virginia T. Weeks, Brooklyn: We reported four cases of erythema multiforme exudativum in 1953, under the age of 6 years, the youngest 14 months. I agree with the speaker that this is a selflimited disease in which the hormone therapy does not change the ultimate course, but it definitely shortens it.

Our cases were acutely ill, and within 24 hours of onset of hormonal therapy the temperature was normal and the children had a sense of tremendous well being. One of the sickest cases, the 6-year-old, had a generalized lymphadenitis, apparently responsible for the signs of a very acute abdomen which, fortunately, the surgeon did not wish to explore.

On that patient, the skin manifestation was an iris lesion. He was the sickest of the four children. He went on to develop a murmur, myocarditis confirmed by electrocardiogram. His course in the hospital was longer than the other three. The total average stay in the hospital was 14 days. We had no severe eye complications. All cases responded very well to the hormone therapy.

Environmental Factors in Childhood Lead Poisoning. Dr. J. Julian Chisolm Jr., Baltimore.

The purpose of this report is to present data which throw new light on the interrelationship among the environmental factors which are important in the production of lead poisoning in children as seen in the urban slum areas of Baltimore. In the light of these environmental factors the effectiveness of chemotherapy upon the long-term outcome of this disease can be measured.

Data were obtained upon the following environmental factors: (1) intensity of exposure, (2) duration of exposure as it relates to the seasonal factor, (3) secondary case rate in housemates of index cases, and (4) the relationship between the incidence of severe permanent central nervous system residua and reexposure to lead among survivors of an initial episode of acute encephalopathy. The data are based upon the study of 193 children exposed to lead, including 89 patients with acute encephalopathy.

Data on the intensity of exposure were obtained in a home study of 30 children under 6 years of age in 10 households, utilizing fecal lead output as an index of lead ingestion. In the subjects with lead intoxication the mean fecal lead output was 44.0 mg/24 hr. Among the nonaffected environmental controls mean fecal lead output was 0.832 mg/24 hr. This represents a fiftyfold difference in lead ingestion. In addition to the index cases, unsuspected secondary cases were found in five of the six subjects aged 12-35 months in this home study.

The probable duration of exposure to lead in patients with acute encephalopathy was found to be three to five months or greater. When the exposure exceeds three months, the advent of summer is the principle precipitating factor in acute encephalopathy. If the child's ingestion of lead begins during the late summer or winter, encephalopathy does not occur until the following summer, and there is no significant correlation between duration of exposure and severity of disease. Irrespective of type of therapy during the acute phase, there is statistically a significant association between the occurrence of severe permanent central nervous system residua and known reexposure to lead following recovery from either mild or severe lead encephalopathy.

The present therapy of acute lead intoxication consists of one or more courses of edathamil calcium repeated at 10-day intervals until biochemical evidence of toxicity disappears. Urinary coproporphyrin output was found to be the most useful biochemical index not only of toxicity but also of whether a second course of edathamil calcium would produce a significant increment in urinary lead excretion. The long-term effectiveness of any therapeutic program is dependent upon the scrupulous prevention of reexposure to lead once the patient is discharged from the hospital.

DISCUSSION

DR. RANDOLPH K. BYERS, Boston: I should like to congratulate Dr. Chisolm on this beautiful paper; I think he has brought out several very important points.

As you all know, I have been interested in lead poisoning for a long time; and it seems to me that one of the most important points to be made is that, as interest in the recognition of the disease increases, the number of cases seen in any locality seems to increase.

When I first was interested in this subject, there were a number of cities in the country which were said not to have lead poisoning. This was supposed to be due to a lack of lead paint in the houses, or something of that sort. But, as people in these cities have become interested, the reports of cases have increased from 25 to 30, 40, 50 cases.

This disease is one which should, of course, be completely preventable, and is one which is entirely man-made.

As far as our cases are concerned, we did have a few encephalopathies in months other than summer months, but, in general, we would agree with the figures shown. It is worth considering, however, the diagnosis of lead encephalopathy in months other than summer months.

The other point I should like to make is to reemphasize this reexposure business. We do run into that a good deal. In the cases which Dr. Lord and I reported, we purposely excluded all the children whom we saw during that period with severe lead encephalopathy. Those were children who were not supposed to have had encephalopathy while in the hospital, and were supposed to be recovering. If we include the children in that group, there were a number who were reexposed, I am sure, and to prevent reexposure is an extremely difficult matter.

We have found, in the first place, that we have no legal lever in Boston which we can use to prevent reexposure. We cannot strip the paint off the inside of buildings belonging to a landlord who does not wish to have it done. We find it very difficult to get the parents to do this in their own houses, too.

In certain instances, where we have had paint removed from houses, the children have gone to other houses and have eaten paint, so that it has been necessary to move some of the children from the slum districts into some of the new housing developments in order to prevent reexposure.

Covering the painted edges with a type of metal stripping which can be put on the edges of counters in people's kitchens, and so on, is one way we have had some success in stopping the nibblers; but I think the children who eat the flakes of paint which fall off ceilings and places probably get the worst lead poisoning, and they are the ones for whom it is of the greatest importance to remove paint entirely.

Finally, I should like to say just a word about the use of Versene by mouth to prevent lead poisoning.

We had one experience which happened accidentally in the hospital. We were trying to get some figures on a comparison between intravenous or subcutaneous use and oral use of Versene.

One child was admitted, and I said, "This child looks in good shape. This would be a good one on whom to find how much lead we can get out by use of oral Versene."

Somewhere along the line in the discussion, we got short-circuited, and I did not impress on the house officer the importance of being sure this child was emptied of lead from the gastrointestinal tract.

About 12 or 18 hours after the use of oral Versene, this child went into acute lead encephalopathy and was made very much worse. I am sure that the use of oral Versene when the gastrointestinal tract is full of lead increases the hazard of acute encephalopathy.

DR. ANDREW D. HUNT JR., Flemington, N. J.: My comment, I guess, is not pertinent to the basic theme of this paper. However, I have been somewhat disturbed (not knowing much about the subject) by the frequent statement that severe behavior disturbances are a sequel of lead poisoning or encephalopathy.

If we think of pica as an emotional disturbance, and if we think that children who consume lead tend to have pica, can it not be that we are dealing with a sequel of the basic emotional disturbance?

It also brings up the possibility that an important factor in the prevention of some cases of lead poisoning would be pediatric diagnosis of pica and trying to work with that situation at the same time that one deals with the removal of the toxic substance in the home.

DR. BENJAMIN KRAMER, Brooklyn: The aggravation of symptoms of lead poisoning during the summer months reminds one of an analogous situation which occurs with so-called latent tetany. During the summer months, tetany becomes manifest, and convulsions occur. This is, in many instances, due to a rise of the serum inorganic phosphorus and to a drop of the calcium level which occurs as a result of natural heliotherapy. It may follow inadequate artificial ultraviolet light therapy.

With lead poisoning, the inorganic phosphorus in the blood is low, of course; but, with exposure to sunlight, it is quite possible that it rises, though I do not know what the figures were in Dr. Chisolm's cases. An increase of the Pb×P product may bring about a deposition of lead phosphate in the tissues and thus serve to bring on the acute manifestations of lead poisoning.

The rise in the serum inorganic phosphorus can, of course, be prevented either by administration of a low-phosphorus, high-calcium diet or by the administration of some substance which will tie up the phosphorus in an insoluble form in the gastrointestinal tract. Any cation will serve which can form a slightly soluble phosphate at the pH of the intestinal contents, such as calcium, iron, or aluminum.

DR. LYTT I. GARDNER, Syracuse, N. Y.: Certain patients with abnormal porphyrin metabolism are light-sensitive. Since the metabolism of porphyrins is altered in lead poisoning, I should like to ask Dr. Chisolm if he has any data on the possible relationship between the increased incidence of signs of lead poisoning in the summertime and a state of light sensitivity, being aggravated during those months.

DR. JULIUS B. RICHMOND, Syracuse, N. Y.: I should like to pick up some of the comments which Dr. Hunt has made. I think it certainly is obvious that children who live in the kind of housing described in this study not infrequently experience some degree of lack of stimulation emotionally. Not uncommonly, certainly, their intellectual levels may not be that of groups of children of comparable age living in other circumstances.

However, as to whether this truly constitutes pica, I should like to hear some comment from Dr. Chisolm, since it was my impression that, when he looked into the control group of the run-about age, very young children, some increase in lead excretion was found in that group.

So I think one could raise the question as to whether this is normal behavior in this age group living in this kind of environment. It would be interesting, of course, to know if children who had lived in a more stimulating environment would resort to ingestion of paint flakes as did these children.

I think this raises another question in evaluating sequellae of this disorder. If we use such criteria as intellectual quotients as one very important one, it becomes very significant to know what these children were like before they ingested lead, again because of the factor of lack of stimulation. Historical data in this connection are not very valuable, because many of these parents would have regarded their children as being of perfectly normal development when, under usual test measurements, this might not have been the case, even prior to their developing clinical symptomatology.

DR. FREDERICK W. BARNES JR., Baltimore: May I ask just one short question?

In view of the tremendous importance of prevention in this disease and the difficulties of detection as emphasized by Dr. Byers, I wonder if Dr. Chisolm would comment on whether the coproporphyrin excretion could be used as a test, possibly, in localities where surveys are being made.

I realize, of course, that coproporphyrin is increased in many diseases; but possibly many of these could be eliminated and such a test might possibly be of use.

I wonder if Dr. Chisolm has experienced anything in that direction.

DR. J. JULIAN CHISOLM JR., Baltimore: I wish to thank Dr. Byers for his comments, and I certainly would agree with what he has to say. I think he has stressed one important type of environmental data which is still needed; namely, data on the prevalence of this disease.

I should also say in reply to him that I purposely chose the very severe forms of sequellae, since these can be analyzed statistically with greater accuracy than the milder forms.

I do not mean for anyone to conclude that the encephalopathy survivors listed as having "no sequellae" are without any central nervous system residua at all; what we mean is that they have none of the very severe sequellae.

He emphasized the problem of reexposure to lead. On the basis of past experience, we have come now to this procedure. Before we discharge a child to his own home or to any other home, we analyze the paint in this house. This is the only way in which we have been able to avoid reexposure uniformly.

We have not used CaEDTA orally, except among older children in whom we were sure there was no reexposure to lead.

Dr. Hunt suggests that pica is an abnormal psychological manifestation and that, therefore, lead poisoning is basically an emotional problem. We have tried to point out that one does not have to invoke abnormal psychological factors where flaking, leaded paint is readily accessible, since the amount of paint a child needs to eat in order to be poisoned is so small. This could readily escape detection on the part of the mother.

We have not tried any of the dietary means mentioned by Dr. Kramer. We have no data on this point.

Dr. Gardner asks about the possibility of photosensitivity in relation to coproporphyrin excretion. I believe photosensitivity is related more closely to excessive uroporphyrin than to the excessive excretion of coproporphyrin III. Coproporphyrin III is the principal porphyrin found in the urine in lead poisoning. We have no data bearing directly upon the point he raises.

In answer to Dr. Richmond as to whether our children were of low intelligence, we have psychometric examinations on all children in the household study and on the recently treated encephalopathy survivors. Their intelligence quotients arrange themselves in the form of a normal binomial distribution curve which is well within the normal range. We would agree with him that the ingestion of small amounts of whatever foreign material is available is normal behavior for small children; the "secondary" case rate found in the household group supports this.

Dr. Barnes asks whether the urinary coproporphyrin test is useful as a screening test. This, of course, is used in industry. It is very useful as a diagnostic screening test in children. However, in chronic cases, the qualitative test is difficult to interpret, especially when the blood lead concentration lies between 75γ and 100γ per 100 ml. of whole blood. A quantitative determination would be much more valuable.

Bronchietasis in Childhood: A Study in Prognosis. DR. A. WHITE FRANKLIN, London.

Two hundred children diagnosed as cases of bronchiectasis have been studied over a period of 5-10 years to see what is the effect of the disease and of its treatment, medical or surgical or both, on the course of the child's life. The cases have been divided into groups labelled ill, invalid, and well, depending on how much disability is present and how much interference there is with normal school life. An attempt is made to correlate this assessment with the following factors:

1. The age of onset of symptoms.
2. Social status with particular reference to housing conditions.
3. The presence of gross disease of the upper respiratory tract.
4. The distribution of bronchiectatic lesions.
5. The method of treatment.

The survey supports the view that symptoms are severest in the early years of childhood, with progressive improvement leading to relative or absolute freedom from symptoms in adolescence. The present health of those who have been treated surgically is compared with that of those who have not had a surgical operation.

DISCUSSION

DR. DONALD CHEEK, Cincinnati: I should like to commend Dr. Franklin on his paper.

I should also like to make the comment that, in Australia, bronchiectasis is not an uncommon disease, and one of the commonest predisposing conditions which leads to bronchiectasis is pink disease, or acrodynia.

I should like to ask Dr. Franklin whether he has looked into the early history of some of his patients and has found a high incidence of acrodynia.

DR. D. J. CONWAY, Ottawa, Ont., Canada: I should like to add my view to Dr. White Franklin's assessment of bronchiectasis. The dilatation of the bronchi is not a progressive affair. Repeated bronchiograms done year after year, or every other year, until the child is past early life into the teens generally shows no change in the bronchial dilatations, in other words, the form is not progressive.

I should like to ask Dr. White Franklin whether he has noticed that the majority of children, as they reach their teens, do have fewer respiratory symptoms and whether some of them do, in point of fact, become quite free of sputum.

It is an important point, this decrease of symptoms as the child reaches into adolescence, because there would be a natural tendency not to subject a child to surgery upon symptomatology improving; yet, if the child is to get maximum benefit, any surgery which is done should be done early.

DR. A. WHITE FRANKLIN, London: In regard to pink disease, I have only seen two cases where pink disease seemed to be involved in the etiology. But it would obviously be occurring at a time when any pulmonary complications would be most likely to lead to bronchiectasis. I am very interested to hear that this is so common in Australia.

I agree with Dr. Conway that many cases do completely lose their sputum, although they may have been producing ounces a day at early stages in life. What I do not know is what then happens to them. I hope I shall live long enought to be able to follow a group through to 40 or 50 years of age. I doubt it.

Then I might be able to come back one day and tell you what happened to them and whether this improvement in adolescence really is of importance.

Placental Parabiotic Circulation of Single Ovum Human Twins. DR. W. G. KLINGBERG, DR. BARBARA JONES, DR. WILLARD M. ALLEN, and DR. EDWARD DEMPSEY, St. Louis.

Improperly functioning parabiosed circulations in single-ovum twins is to be demonstrated. The resulting hematologic abnormalities as well as the effect on body growth in utero will be discussed.

On Nov. 27, 1954, identical twin girls were delivered after an apparently normal full-term pregnancy. The birth weights were 2690 gm. (Baby A) and 1770 gm. (Baby B).

Baby B was noted to be very pale and had hepatosplenomegaly. Total bilirubin determinations were normal. A hemogram revealed Hgb. 3.7 gm. per 100 cc., RBC 1,850,000, WBC 81,900 (uncorrected). The peripheral blood film showed 703 nucleated RBC/100 WBC. An exchange transfusion was performed immediately with 300 cc. of Group A Rh-negative whole blood. The infant showed improvement afterward. The subsequent course was not remarkable, and the infant was discharged with a weight of 2440 gm.

Baby A was normal on examination except for a marked plethora. Transient episodes of cyanosis and respiratory irregularity occurred. Blood studies revealed a Hgb. 25.2 gm. per 100 cc., RBC 7,470,000, and hematocrit 87%. A blood film showed 40 nucleated RBC/100 WBC. By femoral puncture 37 cc. of blood was removed. Three hours later the Hgb. was 24.6 gm. per 100 cc. and hematocrit 82.5%. Over the next two days another 70 cc. of blood was withdrawn. At this time the total bilirubin was 12.3 mg. per 100 cc. The subsequent course of the infant was uneventful.

Both babies and the mother were Group A, CDE, MN. The father was Group A, CDE, N. An indirect Coombs test with the mother's serum and each baby's cells was negative. Indirect

Coombs test with Baby B's cells and Baby A's serum and the reverse was negative. Direct Coombs tests were negative. We concluded, therefore, that no blood incompatibility existed between the mother and the infants or between the two infants.

The severe anemia in Baby B and polycythemia in Baby A suggested that Baby B had been slowly transfusing Baby A in utero. If this concept was true it also would help explain the great difference in body size between the two. The marked erythroblastemia and reticulocytosis of Baby B, coupled with the anemia, could then be explained by maximal bone marrow response.

Examination of the placenta revealed a most unusual condition. By section of the fused amnions a single-ovum placenta was proved by the presence of two amniotic layers separated by one chorion.

Grossly this placenta cleaved apart into unequal halves. The larger half was moderately red, and the vessels forming the cord were not engorged. We believe this portion supplied the blood to the larger polycythemic twin A. The small half had markedly distended veins and was purple-red in color. We believe this portion supplied blood to the anemic Twin B. Perfusion of an artery in each cord with contrasting colored liquids demonstrated arteriovenous shunts between the supposedly separate placental circulations, substantiating a parabiotic circulatory system. This parabiosis must not have functioned equally between the twin circulations to account for anemic versus polycythemic babies. We have to conclude that there was a relative obstruction to the return of venous blood to Baby B accounting for the engorgement of vessels in the placenta and anemia in the baby. This back pressure in turn would extend to Baby A's portion of the placenta through the parabiosed circulations and tend to maintain more blood in Baby A, a resulting polycythemia. This circumstances has not been described previously.

Cord Blood Gas Analyses with Special Reference to Fetal Maturity and Placental Function. Dr. Loren G. MacKinney, Pittsburgh, Dr. Frances Ehrlich, Buffalo, Irving D. Goldberg, M.P.H., and Katherine T. Cantwell, B.A., Albany.

During the past five years cord blood samples from 594 live births have been obtained and chemically analyzed at the Children's Hospital, Buffalo, as part of a longitudinal study of 858 babies. The work of Clifford, Taylor, and others stimulated us to investigate chemical differences in cord blood of premature, postmature, and mature newborn babies. We also wished to assess the ability of the placenta to function as an exchange organ of O_2 and CO_2 in these three groups.

Methods.—Blood was drawn anerobically from the umbilical arteries and vein of cords clamped and divided before or shortly after the baby's first gasp. The O_2 content, capacity, and saturation; CO_2 content and partial pressure; and pH were determined on these samples. Five hundred sixteen placentae were weighed and examined grossly for infarction, premature separation, and other abnormalities. The newborn infants were divided into four groups as follows for analysis: (1) 97 postmature (gestational age of 42 weeks or more), (2) 103 premature (less than 42 weeks' gestation and 5 lb. 8 oz. in weight or less), (3) 633 mature, and (4) 25 babies of unknown gestational age weighing over 5 lb. 8 oz.

Results.—1. No significant differences are found between the groups in cord vein O_2 saturation, CO_2, or CO_2 partial pressure.

2. The postmature infants tend to have larger placentae by weight, and these have a higher incidence of moderate to severe infarction.

3. There appears to be a direct relationship between the weight of a baby's placenta and its cord-vein O_2 saturation.

4. There is indication that babies with infarcted placentae have lower cord-vein O_2 saturation and higher O_2 capacity than those with no placental complication.

Conclusions.—These data indicate that (1) there is no significant difference in the cord blood O_2 and CO_2 values of babies with reference to their maturity per se, (2) the weight of functional placental tissue seems more important than gestational age in determining the blood O_2 saturation of viable fetuses, and (3) large infarctions may impair the efficiency of the placenta to supply oxygen to the baby.

Kernicterus and Prematurity. Dr. Beryl Corner, Bristol, England.

Seventy-two babies dying in the neonatal period with kernicterus as the predominant post-mortem findings have been studied. This has been the principal cause of neonatal death in pre-

mature infants surviving three days. Blood incompatibility has been fully excluded. Sixty-seven infants were premature by both birth weight definition and calculated maturity. Five infants weighed more than 2500 gm. at birth, but three were of only 36 weeks' maturity.

The clinical features of this syndrome are described. The main features are sudden onset on the fourth to seventh day of lethargy, respiratory abnormality, vomiting, and alteration of muscle tone. The infants died 12-48 hours later. During the period of this study, some survivors with identical symptoms have presented with typical neurological sequelae later.

Clinical etiological factors have been analyzed. There was no significant incidence of pregnancy or labor complications, but all the infants presented certain clinical features during the first three days of life, such as severe edema, extensive twitching, vomiting or cyanotic attacks, suggestive of cerebral edema, and other responses to hypoxia. All recovered from these signs before the development of kernicterus.

Postmortem examinations revealed yellow staining of the brain, most intense in the basal nuclei. Nerve cell groups may be conspicuously jaundiced without any histological evidence of cell damage, but death of nerve cells always occurred in certain sites, namely, Ammon's horn, globus pallidus, and subthalamic nuclei, and occasionally in the olives. Greatly increased vascularity always occurred in these areas.

Brains of 16 infants dying in the first few days of life from other conditions were studied as controls. Although some of these infants were severely asphyxiated and survived three days, no changes could be found in the brain cells of the basal nuclei other than slight pallor of Nissl staining.

Certain conclusions may be reached from this study:

1. Intense bile staining of brain tissue may occur without damage to nerve cells in the newborn premature infant.

2. The damaged areas of brain in kernicterus of prematurity are the same as those of kernicterus of hemolytic disease.

3. Death of nerve cells in these areas does not appear to occur from asphyxial changes only in the first three days of life.

4. The presence of high levels of blood bilirubin in addition to some other metabolic disturbance which produces clinical symptoms in the first three days of life seems to be necessary for the death of cells in the areas affected. Increased vascularity of these areas is a constant feature histologically and may represent a response to hypoxia.

DISCUSSION

Dr. Wolf W. Zuelzer, Detroit: Dr. Corner made a very important contribution in calling attention to the occurrence of kernicterus in infants without demonstrable blood-group incompatibility, and she is now calling our attention to the still very substantial incidence of this condition and some of the mysteries connected with it.

I am very deeply interested in the incidence of kernicterus under these conditions. The thought that this brain damage has something to do with hypoxia, and just what the relation is, is a very appealing one, and I think Dr. Corner deserves a great deal of credit for this careful comparison of brains which she has made between kernicterus and asphyxia.

Whether one can recognize the presence of relatively early cytologic damage by morphologic methods is a question which, of course, bothers the morphologists a great deal, and I wonder whether it is actually possible to say that the given cell has been partially, let alone irreversibly, damaged by the type of observation we can make with the microscope. The whole sequence of events which Dr. Corner herself has demonstrated and my own observations lead me to feel that this is indeed bilirubin encephalopathy. The type of data Dr. Corner has furnished us indicate that very strongly. We are agreed that far. But whether it is possible for brain tissue to be this deeply stained without functional damage is a question I should like to leave open. Perhaps we need entirely different methods for their recognition.

In our own material, we have been interested in the fact that, over the years, the incidence of kernicterus, both clinical and pathologically recognizable kernicterus, has declined in a nursery in which, as far as we know, there have been no changes in the management of the premature infants.

That is interesting, because I happen to have received a reprint from Dr. Bakker in the Netherlands just very recently which throws a new and disturbing light on the situation.

In a group of 172 normal and healthy premature infants in whom blood-group incompatibilities were excluded, he found 62 cases of what he calls icterus gravis, and, of these, there were 21 fatalities which were proved by autopsy in 14.

These premature infants were taken care of in high oxygen concentrations, averaging 60%. By comparison, the control group comprised 139 cases of equally normal premature infants, again without blood antagonism, with 7 cases of icterus gravis and 1 case only of kernicterus which was proved by autopsy.

The discrepancy here is so extraordinary that it is hard to disregard the possible connection out of hand. It is, in fact, far more striking than in retrolental fibroplasia.

I think it is not yet possible to evaluate this material, but it is true that, in the material I have had occasion to observe myself, anoxia has played no particular role. The patients were usually premature infants who seemed to get along fairly well; there may be certain differences in our material and that described by the Dutch author, Dr. Bakker, and also in the material Dr. Corner has referred to.

So I think a great deal more attention has to be paid to the basic physiologic mechanism in this condition.

I should also like to say that, in our original material, which was very similar to Dr. Corner's, there was a much higher incidence of ABO incompatability. Of course that material has been excluded in the study which Dr. Corner has reported; but it is still a point worth mentioning that, in apparently otherwise silent or very mild hemolytic disease due to erythroblastosis, the premature infant is in particular danger.

Dr. Sydney S. Gellis, Boston: I am very interested in what Dr. Zuelzer has just said, because there are frequent references now in the literature, though I have not seen them backed up by any data, that the incidence of kernicterus is higher in infants who are maintained in oxygen. I should like to see control data of such statements.

I should like to ask Dr. Corner what percentage of the babies she studied showed clinical icterus within the first 36 hours of life. We are convinced that any baby, premature as well as full term, who becomes clinically icteric in the first 24 to 36 hours of life should be very carefully followed, with checking of bilirubin levels, so that we can prevent this kind of complication and this kind of death. We are fully convinced that exchange transfusion in these infants will prevent kernicterus.

Prof. Guido Fanconi, Zurich, Switzerland: We have seen in premature infants a form of severe icterus without any incompatibility of the blood between the infant and his mother, and characterized by blood inclusions in the red cells, similar but not identical with the vital granulations (Innenkörperanämie). These cases have been described by Gasser. May I ask you if some of your cases, perhaps, would have to do with this form?

Dr. Mary V. Crosse, Birmingham, England: We have studied 60 cases of kernicterus in premature babies in which blood incompatibility has been excluded. (I hasten to say that this is out of 2608 babies, the majority of which weighed less than 2000 gm.)

The first point I should like to make is that the incidence of the disease increases as the birth weight and maturity decrease, and that is particularly the case if you take babies at risk, that is, the babies who are still alive at the age of 48 hours.

Secondly, we have done a series of serum bilirubin levels and obtained the mean bilirubin levels for each birth weight group during the first six days of life. The level rises highest and the peak is latest in the smallest birth weight group.

As in Dr. Fanconi's series of cases, all our babies who developed kernicterus had high serum bilirubin levels, but the level tends to fall if the baby becomes moribund.

Anoxia was a very prominent feature among the babies who developed kernicterus; there was an excessive incidence of antepartum hemorrhage, birth asphyxia, and difficulties after birth. Our incidence did not increase during the short period when we gave excessive oxygen.

Dr. J. Robert MacLean, New York: We have been studying kernicterus and prematurity during the last six months on 85 premature babies admitted to our premature unit on low oxygen.

We have a scattered birth weight rate, and the incidence of kernicterus is relatively the same in all groups. We do have a large number of small premature babies.

We did bilirubins daily on all the premature babies, and the slide shows bilirubins done on the babies with kernicterus at autopsy. You will notice that eight of the nine babies in the premature group who did have kernicterus had bilirubins less than 16 mg. per 100 cc., and some

were in the range of 12 mg. per 100 cc. This would further indicate that biilrubin alone may not be the sole cause of kernicterus in the premature infant, and that other causes for this lowered resistance to bilirubin should be searched for.

DR. ALAN MONCRIEFF, London, England: I got up to ask a question. We have a theory that there may be a toxic factor here, which might be vitamin K. The story is that one of Dr. Corner's assistants went to another city and promptly got four cases of this condition in premature babies. The essential difference was that he had introduced a very high daily standard dosage of vitamin K. I want Dr. Corner to give her views on whether possibly the amount of vitamin K used in Bristol could be a toxic factor in producing this condition.

DR. ROBERT COOKE, New Haven, Conn.: I have a very simple question, what is the number of blood cultures taken in this group of patients?

DR. BERYL CORNER, Bristol, England: There are a great many questions to answer.

All I can say to Dr. Zuelzer is that I think his observations are very important. We have the gross evidence of death of nerve cells, and we know that they do not regenerate. Functional changes in mildly affected nerve cells we know nothing about at present.

To Dr. Gellis, about half our babies were were jaundiced in about 20 to 48 hours. We have been giving a few exchange transfusions to babies with rising bilirubin in the second day of life, but not during the major part of this study.

To Professor Fanconi, there was no evidence of anemia in any of our babies, and we had none of the changes in the blood cells suggestive of a hemolytic anemia.

Professor Moncrieff inquired about vitamin K. We have been one of the places where fairly high doses of vitamin K have been given; but it is a curious thing that, during the last two years, in one of my premature nurseries where no differences in technique have been observed at all, except possibly lower oxygen concentrations, we have not had any deaths from kernicterus during that period, despite the same incidence of small babies. So I do not think vitamin K is more than a small contributing factor.

In regard to blood cultures, they were done on a large number of these babies, and no significant abnormality could be found.

The Heterozygous State in the Hereditary Molecular Diseases. DR. DAVID YI-YUNG HSIA and DR. W. EUGENE KNOX, Boston.

The hereditary diseases, or certainly those which have been recognized by some biochemical abnormality, can all be fitted into a class of "molecular diseases" in which the basic abnormality resides in a large and specific functional molecule. This functional molecule mirrors the pattern as received from previous generations in a gene, and it sets in motion a train of biochemical, physiological, and pathogenetic consequences, which we recognize as the clinical signs and symptoms of the disease. The molecular disturbances can range all the way from a disturbance in the synthesis of a protein, as in afibrinogenemia, to a change of its structure, as in sickle-cell anemia, and to a disorder in a specific renal transport mechanism, as in cystinuria.

The present paper will discuss the detection and significance of genetic carriers of the trait (the heterozygous state) in the hereditary molecular diseases. The literature has been surveyed for evidences of changes among the parents, siblings, offspring, and near relatives of patients known to have a hereditary molecular disease, to determine if the asymptomatic carriers of the abnormal gene might be differentiated from the population as a whole. Of the 39 diseases studied, 18 were found to show clear-cut changes in the heterozygote. This meant that although they appeared to be recessive clinically, the trait could be detected by means of careful biochemical measurements. Eight others showed borderline changes, which were characterized by some abnormality in one of the secondary manifestations of the disease. Six showed no evidence of biochemical abnormalities in the heterozygote, and in seven others no such studies had been undertaken.

A demonstrable abnormality in the heterozygous state is valuable for a variety of reasons. First, it provides a direct means for identifying a heterozygote as a possessor of partial abnormality resulting from one normal and one abnormal gene. This eliminates the need for the distinction between dominant and recessive conditions in the carrier, which simply depends upon the precision with which the character can be detected. Second, changes in the heterozygote help to identify which are the basic and which are the secondary mechanisms responsible for the defect in these diseases. Third, it is useful in estimating the incidence of each of these defects in the population as a whole and in identifying the carriers. By being able to predict

ahead of time the possible occurrence of a disease in the offspring of a certain mating, preventive measures can be instituted and treatment of affected individuals can be started immediately after birth. Finally, the identification of the heterozygote is helpful in differentiating between conditions of genetic and environmental origin.

The frequency in the general population of heterozygotes of even rare diseases may be 1 in 100 to 200. The physiological abnormalities of these individuals, while inconsequential under normal conditions, may become important during illnesses and may play some role in the susceptibility and response of humans to disease itself.

DISCUSSION

DR. LYTT I. GARDNER, Syracuse, N. Y.: We are indebted to Dr. Knox for reviewing this extensive field for us in such a limited time. I should like to make comments which fall under two headings: one, the rational basis for studying heterozygosity, and the other would relate to the concept of molecular disease. What I shall say applies just as well to Dr. Childs' later presentation as it does to Dr. Knox's.

It is most important that we acquire further knowledge about the heterozygous state in man. Dr. H. J. Muller wrote an extensive review a few years ago, called "Our Load of Mutations," which took up his concept of the importance of the heterozygous state (*Am. J. Human Genetics* **2**:111-176, 1950; also cf. *Am. Scientist*, Vol. 38, Pt. 1-3, 1950).

We must be continually reminded of the fact that, since the level of ionizing radiation is certainly not decreasing in the world, there is every reason for us to have a more adequate insight into these heterozygous genes which we bear and to know more and more about the quantitation of the heterozygous state in our population. Such studies may permit us eventually to map the loci on human chromosomes, much as was done with the fruit fly years ago.

My other comments relate to this concept of molecular diseases. This concept, I believe, represents a revolution in our thinking about our own microscopic anatomy. It has been exactly 100 years since Virchow first published for the medical world his concept of *omnis cellula e cellula* in Würzburg, the concept of the cell being the independent unit of the body, and the microscopic structure to which we should look as the unit of disease. He had been stimulated to develop this concept by the biologists Schleiden and Schwann and by his old professor Johannes Mueller. We have had a century of cellular pathology; we are on the threshold of a new approach; we are moving into a new microcosm, and now we must study molecular pathology. Virchow used to urge his students to "learn to see microscopically." It is now up to us to learn to see molecularly.

DR. GEORGE M. KOMROWER, Manchester, England: I was very interested in this paper, as we have been investigating the inheritance of galactosaemia. We have carried out galactose tolerance tests on members of the families in which the condition occurs. I think it comes within the group described by Dr. Knox.

But one thing is quite apparent. As far as we are concerned, the galactose tolerance test is not an entirely satisfactory one, and I imagine that what is going to be the great problem in each of the conditions concerned is that one will have to find the right tool of research in order to find the answer to the problem.

It would seem to us, as a result of the studies I reported yesterday, that maybe we have, in fact, discovered a new method of investigation which would identify galactosemia once and for all as one of these heterozygous conditions. I think Dent, too, discovered that the finding of cystinuria itself is not in any way an adequate answer to the problem of heredity in cystinuria; he has had to take into account certain other amino acids in the urine, too.

DR. MILTON RAPOPORT, Philadelphia: I do not think Dr. Knox meant to differentiate sharply the morphologically inherited differences from the biochemical ones by the table of inborn errors of metabolism. Even as uninspiring a structural detail as which end of us is up and which end down is rooted in biochemistry, for example, the demonstration by experimental embryologists of geneticaly determined organizing enzymes responsible for the head and tail ends of the organism.

It will take a lot of fine sieving to separate out those defects limited to the very periphery of the organism, that is, operating solely as biochemical derangements limited to the level of cellular activity alone, and label them molecular diseases. The term can be used at every level, since enzymes (and individual molecules) appear to condition the state and position of organs, regions of the organism, and the state of organization of the entire organism.

DR. CARL H. SMITH, New York: The concepts elaborated by Dr. Knox find a fruitful application in hematology. The examination of the blood in the parents and siblings of a severely affected individual for evidences of the carrier state has resulted in the detection of the heterozygous individual. The discovery of the trait, such as the presence of abnormal hemoglobin or evidences of Cooley's anemia, has led to considerable interest in the quantitative aspects of inheritance. For example, in sickle-cell-thalassemia disease, the patient may reveal a sickle-cell hemoglobin percentage of 60%-80%, whereas this component is present in amounts below 50% in one of the parents. The same discrepancy, which applies to other abnormal hemoglobins, prompts a consideration of penetrance and expression of a particular gene. It is possible that the simultaneous presence of a second blood factor transmitted from the other parent serves as an augmenting influence.

Does Dr. Knox have any ideas at this stage of his studies concerning the factors involved in the penetrance of genes and the variations in expressivity of a trait?

DR. EDNA H. SOBEL, Boston: I have been very much tempted by Dr. Knox's synthesis and, at the same time, tempted to resist it, at least temporarily.

I should like to comment especially about hypophosphatasia and its association with bone disease, which was not mentioned but I believe was present in the cases studied.

I wonder whether we can be really sure that there is not a toxic substance involved, which may have impaired the enzyme system in the parents and expressed itself as a disease in the child. I do not believe that is true, but am not sure how to exclude it.

Dr. Fuller Albright has recently been studying a 40-year-old man whose bone disease did not begin until his twenties, who has low serum alkaline phosphatase activity, and whose children are deficient in the enzyme but are free of bone disease. Perhaps Dr. Knox can offer an explanation.

I should like to express an absurdity which I do not beileve and I am sure no one else will, which has recently occurred at the Children's Hospital in Boston. There is an instance of lead poisoning in a 5-month-old breast-fed infant. The child's mother also has lead poisoning; however, no lead was found in the breast milk. Did we not know better, we would perhaps consider that this might represent an inherited molecular disease.

DR. W. EUGENE KNOX, Cambridge, Mass.: I should like to second Dr. Gardner's discussion of molecular disease.

In this day, with biochemistry's large contribution to medicine, it takes us but a moment to recognize that almost all of the diseases, if we understood them, would be molecular. For this reason, we have restricted ourselves to the hereditary diseases and we emphasize the fact that it is these biologically elite molecules which are special. They are not made from the diet, and so on; their pattern is transmitted from generation to generation. Primarily because of them the organism lives.

The mapping of genes and chromosomes is something which must be of interest to the geneticist. I am primarily concerned with the individual, who is not at all a good genetic subject. How his abnormalities are reflected in his disease seems to me to be, at least medically, a more interesting thing to spend one's efforts on.

But I do want to reemphasize what Dr. Gardner says, that today we should begin thinking molecularly. This is exactly the type of thinking Dr. Komrower was mentioning, that it is not sufficient to analyze for galactose or cystine; we must analyze in a functional-tolerance-test sort of way for a function, not a level, just as we would analyze for an enzyme. An altered function is what distinguishes these people from others; it is not just the amount of a small molecule, but the function and general type of a large molecule.

I should like to say again that I am not ready to extend molecular disease concepts to morphological diseases which are inherited. This is a question of timing, and it is not because I do not have faith that eventually we will understand enough embryology to know that chemistry affects structure.

In regard to Dr. Smith's question about penetration, he has put his finger on the one really big clinical problem. Penetrance is a genetic term which covers a lot of ignorance about pathogenesis. It has to do with the problem of biological reserve, for another thing. Penetrance deals generally with the variability of clinical manifestations, and perhaps these variations will be less mysterious when we can measure more and more discrete chemical molecules.

Dr. Sobel brings up the problem about toxicity as an explanation for a number of these diseases. She herself was not able to find that hypophosphatasia was a toxic effect of beryllium.

for example, but she cannot rule it out. This is the dilemma we are all in when we do not have the opportunity of experimental breeding to prove the genetic transmission of one of these conditions. We can only do it by exclusion of other causes, and toxicity remains, in hypophosphatasia, apparently to be excluded.

Vascular Hemophilia: A Familial Hemorrhagic Disease in Males and Females Characterized by Combined Antihemophilic Globulin Deficiency and Vascular Abnormality. Dr. Irving Schulman, Dr. Carl H. Smith, Dr. Marion Erlandson, and Eleanor Fort, B.S., New York.

Pseudohemophilia (von Willebrand's disease) has been defined as a hemorrhagic disease associated with normal clotting time, normal platelets, normal clot retraction, normal prothrombin complex, but with a consistently prolonged bleeding time. Most recent studies have indicated that this syndrome results from a functional and morophologic capillary abnormality, with the coagulation mechanism intact. Sporadic case reports, however, have revealed certain instances in which a definite disorder of coagulation appeared to be present. The purpose of the present report is to characterize a distinct group of cases which, while indistinguishable from pseudohemophilia by clinical and routine hematologic studies, demonstrate a definite coagulation defect in association with vascular abnormality.

The patients studied were seven children (four males, three females) from five different families. All manifested a severe hemorrhagic diathesis with predominant bleeding from nose, teeth, oral mucous membranes, and skin. Clotting times were normal or only minimally prolonged; platelets, clot retraction, and prothrombin levels were normal; anticoagulants were absent. The bleeding times were significantly and consistently prolonged. A moderate, but definite, impairment of prothrombin consumption was found in six of the seven children.

By means of the thromboplastin generation test it was found that platelet function was normal, as were levels of PTC and PTA. However, marked deficiency of antihemophilic globulin was found in six of the seven children. Administration of fresh frozen plasma to one patient, demonstrating the abnormal coagulation status, produced striking improvement in bleeding time, prothrombin consumption, and thromboplastin generation.

Capillary microscopy of nail-bed and conjunctival vessels revealed definite morophologic abnormalities in the children who demonstrated the coagulation defect as well as in the child whose coagulation status was normal. Genetic studies suggested that the combined defect was transmitted as a Mendelian dominant.

It thus appears that the von Willebrand syndrome consists of at least two distinct groups: (1) with vascular abnormality and normal coagulation status (pseudohemophilia), and (2) vascular abnormality plus marked antihemophilic globulin deficiency (designated as vascular hemophilia).

DISCUSSION

Dr. John M. Darte, Toronto, Canada: I should like to commend Dr. Schulman on his paper and to point out that we have a similar case which agrees entirely with him in every respect, except that we have demonstrated the defects in the mother of the child.

It is interesting that, in this case, the mother initially gave no history of bleeding. However, we performed the test as part of the routine investigation and found abnormalities in the bleeding time, the capillary resistance, and in the antihemophilic globulin.

Upon further questioning, the mother admitted she had had a hemorrhagic tendency in childhood.

Dr. Douglas Vernon Hubble, Derby, England: I have had five of these cases investigated by Dr. Briggs in Oxford, and I think there is one clinical point which is worth mentioning which supports the morphological evidence presented this morning. That is that when you get a deficiency of antihemophilic globulin associated with this change in the thromboplastin generation test, the bleeding is spontaneous, or occurs as a result of minimal trauma, and therefore indicates that this is an associated capillary deficiency, as outlined today.

Dr. Irving Schulman, New York: I was delighted to see Dr. Darte's paper and to note that he had been able to demonstrate the defect in a mother as well as in the child. We have been both interested in and disturbed by some of the genetic aspects of this syndrome. As mentioned earlier, in two instances a definite family history of bleeding could be elicited, but coagulation studies on the parents were repeatedly normal. In 1928, Minot described several cases which

appear to be quite similar to those discussed today. The patients were followed for long periods of time, and, as they grew older, the clinical manifestations seemed to become less severe. The tendency toward clinical improvement with advancing age in the von Willebrand syndrome has also been noted by several other observers.

On the comments by Dr. Komrower—it is important to point out that one may get a normal clotting time if the antihemophilic globulin concentration is as low as 1% of normal. This test, then, is a fairly gross one. As coagulation methods become more refined it becomes possible to indentify and classify more and more individuals with clinical evidence of an abnormal tendency to bleed. As to Dr. Hubble's comment, in our group of patients there has been no absolute difference in the tendency to spontaneous hemorrhage in those individuals who have antihemophilic globulin deficiency when compared with the child who does not. Even in the six children who had definite antihemophilic globulin deficiency there was no exact correlation between the assayed antihemophilic globulin levels and the clinical severity. The relative influences of the coagulation disturbance and the vascular abnormality as determinants of severity of disease must still be elucidated.

Virilizing Adrenal Hyperplasia: A Genetic and Hormonal Study. Dr. Barton Childs, Dr. Melvin M. Grumbach, and Dr. Judson J. Van Wyk, Baltimore.

Evidence indicating that virilizing adrenal hyperplasia is a genetically determined disorder has been obtained from a study of 56 families containing 76 affected individuals. All the families have been seen and followed in the endocrine clinic of The Harriet Lane Home. Comparison of the number of affected individuals observed with expectation assuming the disease to be due to a gene manifesting itself only in homozygotes revealed good agreement with this hypothesis. The incidence of the disease is estimated to be about one in 65,000, the frequency of the gene in the population 0.004, and the frequency of heterozygotes 0.008. There was consanguinity in but one family, an incidence which agrees well with expectation. The presence of the gene in parents did not alter fertility as measured by family size or miscarriage rate. Among the group of affected individuals the ratio of males to females was 0.4. When the index case in each family is removed and the sex of affected sibs only is considered, the sex ratio approaches unity. This suggests that the apparent alteration in sex ratio is due to ascertainment of an excess of girls, principally because of the abnormality of the genitalia.

Examination of the clinical variations of the disorder indicated heterogeneity between but not within families. In 18 sibships containing a patient with the salt-losing defect and Addisonian symptoms early in life, all other affected sibs had this form of the disease. In two families in which one patient showed hypertension, affected sibs also were hypertensive. This phenomenon suggests that more than one gene might be involved, possibly a system of multiple alleles.

Assuming both parents to be heterozygotes, an attempt was made to find minor manifestations of the presumed gene in them. Recent studies from this and other laboratories suggest that a block in the synthesis of Compound F by the adrenal cortex is the fundamental defect in this disease and accounts for the large amount of pregnanetriol excreted by these patients. Twenty parents were given 60 to 80 units of corticotropin-gel (ACTH), and pregnanetriol, pregnanediol, and 17-ketosteroids were measured in 24-hour urine samples collected before and after administration of the drug. Eighteen normal individuals served as controls. The increments of the various steroids following stimulation were then compared. No differences were found between parents and controls in excretion of pregnanediol and 17-ketosteroids. There was, however, a slightly greater rise in pregnanetriol excretion among the parents, the increments showing a mean of about twice the controls. The values were low, and the numbers small, so that the difference was not statistically significant (p=approximately 0.1), but the data suggest a manifestation in possible heterozygotes, which is compatible with the hypothesis that the disease is a genetically determined inborn error of adrenocortical steroidogenesis.

DISCUSSION

Dr. Alfred M. Bongiovanni, Philadelphia: We are very much indebted to Dr. Childs and his colleagues for their investigations into the genetic aspects of this problem. With regard to the pregnanetriol excretion of the parents of these children, although a significant difference is not seen, there does seem to be a trend toward a higher level. As Dr. Childs presented a paper, a thought occurred to me. The genetic defect seems to be a lack of one of the adrenocortical hydroxylating enzymes in the actual disease. In the parents (or heterozygotes) a partial deficiency

of this enzyme may not generally become apparent in the test used, since it is probable that even with the added stimulation of corticotropin, only a relatively small amount is required for the usual conversions to Compound F without the loss of much pregnanetriol. This might mean that we should look for another method of testing. We have done some studies with Dr. Lawrence Schulman at Johns Hopkins, and in patients with presumably normal adrenal function there is no increase of pregnanetriol even after nine months of treatment with corticotropin.

DR. LYTT I. GARDNER, Syracuse, N. Y.: I should like to ask Dr. Childs if we are still justified in telling parents that, on a statistical basis, the chance of having another affected child is approximately one in four. Or do we have to abdandon this rule-of-thumb statement?

DR. BARTON CHILDS, Baltimore: In answer to Dr. Gardner's question, I should think there was no indication from this data that the probability of further affected children in a given family would be anything but one in four.

Studies in Sickle-Cell Anemia: VII. Blood-Volume Relationships and the Use of a Plasma Extender in Sickle-Cell Anemia; A Preliminary Report. DR. MELVIN E. JENKINS and DR. ROLAND B. SCOTT, Washington, D. C.

This investigation comprises an evaluation of plasma and red cell volumes before and after infusions of whole blood with a comparison of the effects of a plasma extender, 6% dextran in 5% fructose, under similar conditions in 18 Negro children with sickle-cell anemia. Total circulating hemoglobin mass values were used as the chief reflections of hematologic variations. In addition, clinical manifestations were carefully observed for changes in activity following the infusions. Blood-volume determinations (modification of Evans Blue dye [T1824] method of Gregerson) were made on 18 nonanemic children as controls. In addition, two symptomatic sickle-cell patients received daily blood-volume determinations without the administration of any intravenous therapy.

The average total blood volumes in the study group were found to be similar to control blood volumes, with the abnormally high plasma volumes of the study group tending to compensate for lowered cellular volumes.

Total blood volume rise 24 hours after varying amounts of whole blood averaged 19% of the initial blood volume, with a wide range of increase in the nine patients studied (0.2% to 63%). We observed an average increase of 47.4% in total circulating hemoglobin following blood transfusion in the same subjects. In five of the nine transfused patients the total hemoglobin rise was more than could be explained by the quantity of transfused hemoglobin. It is postulated that blood transfusions increase the total circulating hemoglobin not only by the extrinsic effect, but also by mobilization of stagnant intrinsic erythrocytes from certain organ depots and splanchnic areas.

There was a 10.5% increase in the 24-hour blood volume and a 9.4% increase in the total circulating hemoglobin in the nine patients with sickle-cell anemia who received intravenous dextran. Six of these patients showed definite clinical improvement.

The therapy of sickle-cell anemia is essentially symptomatic. It appears that the enhancement of blood-vessel tonus, the increase in total blood volume, improved tissue hydration, and mobilization of some of the patients' stagnant or trapped sickled cells may account in the main for the beneficial effects of blood transfusions. Our preliminary observations suggest that 6% dextran in 5% fructose may supply similar benefits in crisis states of this disease and at the same time eliminate certain specific hazards of repeated blood transfusions. No untoward, allergic, or toxic reactions were noted following dextran administration.

DISCUSSION

DR. CARL H. SMITH, New York: Dr. Scott's presentation was particularly interesting to us because we are at present guided in treating the sickle-cell patients by blood-volume determinations. Treatment of the crisis is frequently a vexing problem because of difficulties in diagnosing this state. We are led to believe repeated blood-volume studies may throw some light both on treatment and diagnosis.

We have found that the blood volume in normal children coincides with that of adults, namely, about 75 to 80 cc. per kilogram of body weight for the whole blood, 45 cc. for plasma, and 35 cc. for red cells. In eight children with sickle-cell anemia who were not in crisis, the average blood and plasma volumes were inordinately high, 104 and 83 cc., respectively. These

values are to be compared with those in iron-deficiency anemia, in which the plasma volume increases, but only to the extent of maintaining a normal blood volume. Our experience has been that during a sickle-cell crisis, the plasma volume drops sharply to an average of 70 cc. and the total blood volume to 89 cc. It was not possible to determine whether shrinkage in plasma volume precipitated the crisis or whether it accompanied some more direct etiological factor. Be that that as it may, the restoration of expanded precritical blood and plasma volumes was associated with recovery. A variety of treatments were utilized, which included water by mouth and infusions of glucose, plasma, and dextran. While the latter two seemed most efficacious, they still have to be evaluated with a larger experience. In one child in whom the clinical picture simulated a crisis but in whom the blood and plasma volume had not decreased, it was found that the condition was a Salmonella infection. These observations may prove of diagnostic importance and are worth while exploring on a larger scale.

Dr. James N. Etteldorf, Memphis: As Dr. Smith indicated we have observed similar changes in total blood volume and plasma volume and extended our studies to include the determination of the cardiac output. The data which are given in the abstract are not as complete as at the present time; we have found to our amazement that the cardiac output is, on the average, doubled in these patients, even out of crisis.

Therefore, I should like to ask if Dr. Scott has observed any ill effects following the administration of plasma extenders as far as cardiac function is concerned.

The observation that the hemoglobin concentration was so remarkably elevated by transfusions impressed me. In our experience, particularly jn patients with severe anemias, we have been quite unsuccessful in getting as marked an elevation in the hemoglobin following transfusions. I wonder how much blood was given to these patients.

Dr. Charles Pryles, Boston: I should like to ask Dr. Scott if he has done any studies on serum or red blod cell electrolytes on his patients. At the same time, I should like to ask Dr. Smith if his little patient with Salmonella dysentery thought to be in sickle-cell crisis was not in a state of acidosis when seen.

At the Thorndike Memorial Laboratory of the Boston City Hospital we have a little girl in whom we have been able to precipitate a crisis by producing a state of acidosis and then to take her out of crisis as soon as we could correct her acidosis. We have been able to repeat this on three occasions in all and are just beginning to study the role of serum and red blood cell electrolyte changes in the precipitation of so-called crises.

Dr. J. Randolph Sharpsteen Jr., Philadelphia: We feel, in our studies, that not expanding the blood volume but expanding the cell volume from cell to cell is important. Therefore, we hydrate patients by mouth to cause a decrease in plasma osmotic pressure; and, with this decrease in plasma osmotic pressure, we feel we can return the morphology to a more normal type.

It is not capillary expansion; I doubt whether we could expand all the total amount of capillaries with the volumes given.

Were your patients in crisis at that time?

Dr. Roland B. Scott, Washington, D. C.: With respect to Dr. Smith's statement about oral hydration, we have tried this method in a few cases, but we have not had too much success with it. During a crisis these children often exhibit anorexia, and it may be difficult to get them to take large quantities of fluid by mouth.

I think that isotonic dextrose solution given intravenously may be helpful for the emergency treatment of certain crisis episodes which theoretically may result from stagnation of sickled cells. Of course, we have to keep in mind that some crises apparently abate spontaneously without therapy.

Dr. Etteldorf spoke about the ill effects of sickle-cell anemia on cardiac function. I think his comment is quite apropos, because one has to be very careful to avoid overloading the circulation in children with sickle-cell anemia. We gave our dextran slowly, often taking as long as three to four hours to give 500 cc.

There was a question about the amount of blood given. The dosage of blood was roughly 10 cc. per pound, given slowly and with care to avoid cardiac embarrassment.

Dr. Pryles, I believe, asked about electrolyte studies and the effect of acidosis. We have not carried out systematic electrolyte studies in our cases; however, I believe that acidosis is in some way related to a crisis. The role of acute infections in precipitating crisis episodes may possibly be mediated through changes in acid-base equilibrium.

I think the comment about increasing the cell volume through oral hydration is very interesting. However, in my opinion this method of therapy also has its limitations. In severely anemic patients, the cellular volume of the blood may be as low as 10 cc. or less per kilogram of body weight. It may be hazardous in such instances to depend too much upon increasing the cellular volume of the erythrocytes through the means of forcing water intake by mouth. Under these circumstances, whole-blood transfusions or intravenous dextran infusions may be necessary to pull the patient out of a severe crisis.

On the question as to whether our patients were in crisis, they were in what we term a "clinical crisis," which is characterized by listlessness, anorexia, and muscular pains.

DR. CARL H. SMITH, New York: This child was severely ill with a Salmonella infection, and there were no evidences of acidosis.

Etiological Factors in Congenital Cleft Palate. DR. F. C. FRASER, Montreal, Canada.

Our work on the experimental production of cleft palates in mice by maternal treatment with cortisone, Compound F, corticotropin (ACTH), starvation, and acute folic acid deficiency will be reviewed. The various factors that determine whether or not a given offspring has a cleft palate include dose of teratogen, gestational stage treated, maternal and fetal genotypes, maternal weight, and amniotic fluid pressure. The embroyology of palate closure and the effect of cortisone on it will be described.

The experimental findings in mice will be compared with the clinical findings in the antenatal and family histories of about 200 cases of cleft lip and/or palate seen at the Children's Memorial and Royal Victoria Hospitals.

The risk of recurrence of the same defect in the sibling of a child with cleft lip and/or cleft palate is 3.6%-6.5% for a child with cleft lip (with or without cleft palate) and 2.2%-4.3% for a child with isolated cleft palate.

DISCUSSION

DR. SIDNEY Q. COHLAN, New York: I should like first to congratulate Dr. Fraser on his important contribution to experimental teratology.

I am sure that most of you are aware of the drastic effect on the world population resulting from congenital malformations. It has been estimated that one out of four pregnancies is wasted throughout the world as a result of stillbirth, abortion, and infant death before the first year of life due directly to congenital malformation. Our population, for good or bad, would perhaps be 25% greater if we knew more about the causes of malformations and how to prevent them.

One of the considerations which always arises in these discussions is the necessity of great caution in transposing any experimental work to human experience. However, it seems to me, that implicit in teratologic investigation is the silent suspicion of each investigator that perhaps there is a kernel of human etiology involved in what he is doing in the laboratory.

Experimentally, as far as the human is concerned, it is obviously impossible to set up experimental and control studies for the production of malformations. However, we have recently had an interesting experience in reversing the usual animal-to-human experimental progression by studying the effect on the rat fetus of maternal exposure to active Rubella virus. At present, although we do not have enough data to be too definite, we have observed a significant occurrence of what appears to be congenital hydrocephalus in the offspring of rats whose mothers were injected with Rubella virus intracardially between the fifth and eighth days of pregnancy. So this may be an instance where an agent known to produce malformation in human pregnancy may also induce developmental changes in the experimental animal.

As far as the development of cleft palate in the mouse is concerned, we have been able to produce similar changes in the rat with other agents. The one we have been interested in over the past few years has been vitamin A excess. About 9% of fetal rats whose mothers are given 25,000 to 30,000 units of vitamin A during pregnancy will present facial malformations as seen on the photograph. Most of these animals have associated cleft palates.

In our laboratory we have done some preliminary work with the other fat-soluble vitamins. Vitamin K will produce anomalies in offspring when given in excessive amounts. Vitamin D is not as specific. We have been unsuccessful to date in producing anomalies with excess vitamin E.

We must be very cautious in attempting to advance reasons and explanations for these findings, as we do not, as yet, know enough about the mechanism of malformation to venture too many hypotheses.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: I have been interested in the experimental dosage of cortisone, particularly that often used in studies designed to test its effect on resistance

to infection. As frequently used in animals, it is far in excess of what would be ordinarily used in man. Obviously this is sometimes planned to make sure enough is given. However, it would be important to determine, if possible, the optional dosage under such circumstances.

I wonder if Dr. Fraser would care to comment upon the relationship of the dosage of cortisone to the production of these interesting congenital lesions.

DR. F. CLARKE FRASER, Montreal, Canada: I should like to thank the discussers for their interesting comments.

I certainly agree with Dr. Cohlan about the caution that should be exercised in transferring any of this to humans. I think perhaps we can use this experimental model as a tool to dig up relationships that we might then look for in human data. I would not go any further than that.

Dr. Bradford, I agree with you that the doses we used were tremendous compared to the doses used therapeutically. However, I might also say that the mouse is very resistant to cortisone and that a dose-per-unit-body-weight comparison with humans is probably not valid.

There are certainly a number of cases now where mothers have been treated with cortisone during pregnancy with a successful result as far as the baby goes, but there are also a few cases known of congenital defects occurring in children whose mothers were treated with cortisone during pregnancy. It is too early to tell whether there is any causal relationship. I think the risk of producing congenital defects in humans is probably low if the doses are kept small and the advantage of treatment to the mother might well outweigh this risk. However, if at all possible, I should rather not start treatment until after the 10th week of pregnancy, particularly if there were a family history of congenital defects.

Some Serologic Observations on Hemolytic Disease of the Newborn Due to A or B Incompatibility. DR. VICTOR C. VAUGHAN III and DR. JUAN SOTOS, Philadelphia.

Studies of the incidence and causes of early icterus in the neonatal period have confirmed the frequency of A or B isoimmunization as about 0.8% of newborn infants.

Serologic studies indicate that it is usually possible to establish the presence of hemolytic disease due to A or B incompatibility with confidence through demonstration of abnormal protein attached to the infant's cells and/or examination of maternal serum for "immune" anti-A or anti-B.

These studies have emphasized the wide variability in serologic patterns in maternal serum; they have furthermore shown that it may be important to use the cells of the father of the affected infant in carrying out diagnostic tests on maternal serum, since the cells of the infant are much less reactive and may give negative results in such studies.

DISCUSSION

DR. FRED H. ALLEN JR., Boston: As Dr. Vaughan has indicated, it is difficult to establish the diagnosis in the individual case, and, as his experience in Philadelphia has gone, so has ours in Boston where, in 1950, the relative frequency of A-B-O erythroblastosis was considered to be about 5% of all cases. Now we think it is at least 60%, perhaps even higher. It is therefore an important disease, one of our more frequent diagnostic problems.

The clinical severity of disease is much different from that caused by anti-Rh. Anemia, for example, is rarely present in the first two days of life in erythroblastosis caused by anti-A or anti-B. Stillbirth is almost unheard of.

Jaundice, of course, is the characteristic finding. Undoubtedly, it is somewhat less severe on the average than that caused by anti-Rh, but is severe enough to cause kernicterus in a disturbingly large percentage of these babies.

Any baby who has jaundice in the first day of life, or even in the first 36 hours, should be considered to have erythroblastosis, except in the rare cases where one can make a clinical diagnosis of some other condition. For practical purposes, if the baby does have early jaundice, and if the Coombs test is negative, and if the baby shows an A-B-O incompatibility with the mother, the diagnosis of A-B-O erythroblastosis should be made. Other tests, including tests of serum for anti-A and anti-B, fragility tests, search for microspherocytes in stained smears, and the glue test described by Dr. Vaughan, do not in my opinion significantly increase the accuracy of diagnosis.

I want to make two other points. One is that the estimation of hemoglobin is a risky procedure in erythroblastosis, especially in that caused by anti-A or anti-B, simply because a high

hemoglobin is the usual finding. The other point is that exchange transfusion is every bit as effective in these babies as it is in those whose trouble is caused by anti-Rh, if Type O blood is used.

DR. WOLF W. ZUELZER, Detroit: Our experience in regard to the variability of the maternal antibodies agrees with Dr. Vaughan's data in general, and we have even had the disturbing experience of finding, in a woman who gave birth to three consecutive A babies, all with erythroblastosis, that an antibody present in the first two pregnancies which could not be neutralized, disappeared with the third baby, who had exactly the same manifestations.

However, there are a few differences, some so marked that I can ascribe them only to differences in the techniques we have been using, as compared to Dr. Vaughan's.

One of these may be—and I should like to ask Dr. Vaughan specifically if I understood his data correctly—that we have followed Witebsky in using a standard amount of one-to-one dilution of the neutralizing substance and let the chips fall where they may, rather than attempt quantitatively to neutralize the serum before performing the test.

With that technique, we have not found the same difficulties in neutralizing B as Dr. Vaughan referred to; and we feel that approximately 85% to 90% of the cases give a resonable pattern of "immune" antibodies, so-called, in the mother.

However, that still leaves us with an uncomfortable 15% or 20% or so; and we have gone, therefore, in our diagnostic work, to the baby, and have utilized two or three things with which we feel quite comfortable to work.

One, of course, is spherocytosis, which Dr. Gasser, I believe, was the first one to point out, and to which we pay a great deal of attention and which we have found to be an almost invariable stigma.

The other is to take the serum of the newborn infant—and this is a test the residents can do in the laboratory rather quickly—and use it either for direct agglutination or for the Coombs test, using adult homologous cells as the substrate and O cells as the control. With, I think, one single exception in the last 60 cases or so, that test has been positive; in other words, there is a free antibody against the baby's own blood group present in the baby's sera.

One can go a little further and demonstrate the presence of antibodies by the dilution technique, again using adult cells as a substrate. In our experience, that has been, from the theoretical point, very valuable; but, as a practical procedure in an emergency, of course, it is not.

I should like to reecho the remark Dr. Allen made, that there is, in the untreated case material, a very high incidence of kernicterus, provided you define your disease as manifest and not just merely as incompatibility with some serological abnormality.

DR. VICTOR C. VAUGHAN, Ardmore, Pa.: I should like to thank Dr. Allen and Dr. Zuelzer for their comments.

I would reecho the caution against leaving these babies untreated and a particular caution against following them by levels of hemoglobin. The hemolytic process, as reflected in hemoglobin levels, is certainly not possible to discern in relation to elevation of serobilirubin.

We have had antibodies disappear in our own laboratory. We have seen a mother's serum which had demonstrable antibodies when tested fresh against the husband's cells; but, when both had been in the laboratory for a week or more, the mother's serum frozen and the father's cells as clean as we could keep them in a refrigerator, we have been unable at this time to demonstrate what was so obvious the week before.

This, I think, means again that we should be exceedingly careful in our choice of test cells when we do this work.

In our experience, the neutralization of anti-B has given use the greatest of difficulty; and we have nowhere near the 80% to 90% success with B neutralization which you seem to have the good fortune to have.

I do not know what the differences in technique are. We started out, actually, with the one-to-one challenge which Dr. Levine has, I believe, used with some confidence, and we have been simply unable, in our hands, to get satisfactory neutralization and with some frequency.

Effect of Magnesium Sulfate on the Alterations in Renal Dynamics Induced by Intravenous Hemoglobin. DR. WILLIAM J. A. DEMARIA and DR. JEROME S. HARRIS, Durham, N. C.

A wide spectrum of effects is noted when incompatible transfusion reactions occur. Many of these effects are mediated through changes in the circulation and may be due to either the

presence of free circulating hemoglobin or to the occurrence of an anaphylactoid or shock-like reaction. This study deals primarily with the changes in renal dynamics induced by the intravenous infusion of hemoglobin solutions and the effect of intravenously administered magnesium sulfate thereon.

Three different groups of experiments on dogs are presented. The first group confirms previous reports that intravenous administration of lysed red blood cells caused a significant decrease in the glomerular filtration rate, effective renal plasma flow, and urine flow. For any effective level of plasma hemoglobin concentration, the actual level seems to be of less importance in causing these changes than the rate at which this level is achieved. The second group demonstrates that magnesium sulfate reverses immediately these changes in renal dynamics and urine flow. In the third group it is noted that if a satisfactory level of serum magnesium is established prior to the hemoglobin infusion, the kidney does not suffer a significant change in its function as measured by clearance techniques.

It is concluded that lysed red blood cells or the liberated hemoglobin causes a renal vasoconstriction and that this is effectively reversed or prevented by a known vasodilator, magnesium sulfate.

DISCUSSION

DR. GERALD MILLER, Rochester, N. Y.: I think this is a beautiful demonstration of what a good many people suspected, that the name "hemoglobinuria processes" is very bad, and I am glad to see these data reported.

I have one question with reference to a paper in clinical investigation during the past year by an Australian. I should like to ask the question about a paper published in the *Journal of Clinical Investigation* during the past year, from Australia, in which a group of investigators infused, I believe, red cells into humans, and showed comparable reduction in renal function.

One observation which they added (and, if I remember correctly, without further comment) was that the infusion gave results very comparable to yours when you infused magnesium sulfate. I wonder how these two could be brought together.

I shall ask the speaker to speculate.

DR. WILLIAM J. A. DEMARIA, Durham, N. C.: Thank you for your comments. I am sorry I cannot do anything but speculate, and possibly that might better be done in private.

The Metabolism of Mucopolysaccharides. DR. ALBERT DORFMAN and DR. SARA SCHILLER, Chicago.

Little is known regarding the mechanism of biosynthesis of the acid mucopolysaccharides, hyaluronic acid, and chondroitinsulfuric acid. Utilizing C_1- and C_6-labeled glucose it was possible to demonstrate that both the glucosamine and glucuronic acid components of hyaluronic acid, formed by a strain of Group A Streptococcus, derive from glucose without previous scission of the carbon chain. Experiments employing C^{14}, N^{15}-labeled glucosamine and carboxyl-labeled acetate demonstrated that glucosamine and acetate are incorporated into hyaluronic acid in growing cultures of this organism.

Methods have been devised for the isolation of both hyaluronic acid and chondroitinsulfuric acid in analytically pure form from the skin of both rats and rabbits. The administration of C^{14}-carboxyl-labeled acetate, uniformly labeled glucose, and $S^{35}O^{=}_4$, made it possible to determine the rate of synthesis of both hyaluronic acid and chondroitinsulfuric acid as well as the relative rates of synthesis of various portions of the respective molecules. In both species, hyaluronic acid was found to turn over more rapidly than chondroitinsulfuric acid (the half-life time of hyaluronic acid varied from 1.9 to 4.5 days in different experiments, while that of chondroitinsulfuric acid varied from 5.7 to 10.7 days). When C^{14} uniformly labeled glucose and $Na_2S^{35}O_4$ were administered simultaneously, it was found that the galactosamine and $SO^{=}_4$ portions of chondroitinsulfuric acid turned over at the same rate. Similarly, when both carboxyl-labeled acetate and $Na_2S^{35}O_4$ were employed, the acetyl and $SO^{=}_4$ groups of chondroitinsulfuric acid were metabolized at the same rate. These experiments suggest that the acetyl and $SO^{=}_4$ groups of chondroitinsulfuric acid do not exchange with the respective body pools, but rather that the breakdown of the mucopolysaccharide involves more profound degradation of the molecule.

Studies of the effect of various factors on the rate of mucopolysaccharide synthesis have demonstrated a decreased rate of synthesis of both chondroitinsulfuric acid and hyaluronic acid

in alloxan-treated rats. This was evidenced by a decreased uptake of isotope, a decreased turnover rate, and a decreased concentration of polysaccharide. No such interference with synthesis was observed in fasted controls.

The possible role of insulin in the synthesis of mucopolysaccharides of ground substance is of particular importance in that it may provide insight into the mechanisms of deficient wound healing, deficient resistance to infection, and accelerated vascular degeneration in diabetes mellitus.

DISCUSSION

DR. LAWSON WILKINS, Baltimore: I think it would be of very great interest to see Dr. Dorfman extend his studies to thyroid relationships, as there is evidence that, in myxedema, there may be increased polysaccharides in the skin.

DR. ALBERT DORFMAN, Chicago: I agree very heartily with Dr. Wilkins; it is one of the things we are hoping to do.

Unfortunately, what may not be apparent in the report of these results is that these experiments take a very long time to do and that the doing of one total turnover experiment, with all the isolations and chemical degradations, has frequently taken us as long as six months, with two or three people working.

It is obvious that the possibilities of the things we might now study with the techniques available are very great; we are very much interested in the thyroid problem.

Evaluation of Adrenocortical Active Hormone Therapy in Childhood Nephrosis.
DR. CONRAD M. RILEY and DR. RUTH ALICE DAVIS, New York.

In an effort to evaluate the effects of adrenocortical hormones on the over-all picture of childhood nephrosis we used several approaches. A scoring system was evolved to express in figures the general clinical state. The mean score for the past four winters of our own clinic population of children with active nephrosis has shown steady and significant improvement. This change is felt to correlate with the increasingly aggressive use of the hormones. Next we felt it significant that of 33 patients in our group in whom scheduled treatment was begun in the first six months of disease, though 2 have died, all those living fail to show signs of irreversible renal damage. The mean period of observation of these cases is 17.6 months, with a standard deviation of 7 months.

No change correlated with treatment could be demonstrated in the proportion of "complete cures" to deaths. On the other hand, correlation of treatment with duration of life after the onset of disease showed significant findings. From a group of over 1300 cases collected from 18 clinics we chose patients with onset of edema under 12 years of age who had been seen by the reporting physician within six months after onset. Also, to insure the availability of adequate antibacterial therapy, we considered only patients with the disease beginning in 1946 or later. Our first comparison of percentage survival related to time after onset showed that the per cent of patients alive 30 months after onset was significantly greater in the group treated with hormone on a preplanned schedule with the first 6 months of illness than in either the group without treatment or that given hormone first within 6 months after onset to relieve edema. Because certain bias of selection was feared in this comparison, the "treated by schedule in first six months" group was compared with all other patients not so treated. A χ-square test showed that the greater per cent survival observed at 30 months in the early treated group was likely to have resulted from chance alone less than once in 100 times.

To rule out the possibility of bias because of rare patients who respond unfavorably to treatment even early in the disease and so might never get into the "treatment" group as defined, we compared survival of patient groups on the basis of calendar year of onset without regard to treatment. With such a comparison it was apparent that patients whose disease began in 1951, 1952, and 1953, during which period more and more aggressive therapy has been used, had impressively better survival curves than those with onset in 1946-1950.

From these comparisons we felt we had demonstrated either that nephrosis is changing in severity in recent years or that treatment is significantly modifying it. Because of the abruptness of the change we feel that therapy is a more reasonable explanation.

Lastly we suggested that the sedimentation rate is a useful guide for determining when treatment should be started or stopped. We have found that prolonged treatment with adrenocortical active hormone can often reduce the sedimentation rate to normal. If this measurement is kept

normal by giving repeated treatment when it tends to rise, the patient appears to remain clinically well. Increasing proteinuria or the appearance of minimal edema are also used in deciding when to give further therapy.

DISCUSSION

DR. MILTON RAPOPORT, Philadelphia: I have some comments to make upon what is referred to as maintenance therapy of childhood nephrosis with adrenocortical active hormones. The need to continue the administration of hormones to all children after the achievement of clinical remission of the nephrotic state is not clear, and we feel at times is even unjustifiable. That there are quantitative differences in the severity of the nephrotic syndrome from child to child is quite apparent, even though the estimates of severity are retrospective ones, based largely on elapsed time to death or recovery in any given child.

At the Sixth Annual Conference on the Nephrotic Syndrome, at Cleveland, in November, 1954, Dr. McCrory and I presented some preliminary data, which we believe has bearing on the early assessment of the severity of the nephrotic process and upon the selection of patients for maintenance therapy.

Quantitative measurements of protein excretion were carried out in 35 children with nephrosis, who received cortisone therapy for 28 consecutive days each. In 23 children, proteinuria was abolished after varying intervals of time—in no instance later than 18 days after the beginning of therapy. In 13 children in whom proteinuria persisted for the 28-day period of hormone therapy, there was first a decrease in the amount of urinary protein from initial average values of 6 gm. daily to 3 gm. daily by the 10th day of therapy. This was followed by a gradual rise in protein excretion to an average value of approximately 5 gm. by the 24th day of cortisone administration. The increased proteinuria in the later days of therapy is not a deleterious effect; it is rather an expression of continued clinical improvement. In the presence of a glomerular leak of a smaller, but now fixed magnitude, serum protein formation exceeded glomerular leakage and loss, with resultant gradually increasing serum protein values. The gradual rise in urinary protein excretion reflected the leakage from serums of higher protein content.

From these findings, a basis emerges which serves as a guide in future planning of maintenance therapy. In the child in whom cortisone can effect disappearance of proteinuria, we believe therapy should then be discontinued and resumed only with the reappearance of significant proteinuria. In this way, those patients in whom proteinuria does not recur, or returns only after long intervals, are not subjected to needless prolonged hormone administration. Using the rapidity of reappearance of significant proteinuria as a criterion of the severity (or magnitude) of the disturbance eliciting the nephrotic syndrome, one is now, in a measure, fitting maintenance therapy to the individual patients' requirements.

For the group of patients with persistent proteinuria after 18 days of cortisone therapy we have no recommendations to make as to continued or maintenance therapy. The most that can be said is that it is more difficult to criticize any of the different maintenance regimens than it is to justify them.

Perhaps we are fooling ourselves, but we believe that we can attach some prognostic value to a patient's response to cortisone. If we can seal off a patient's golmerular leak, i. e., abolish proteinuria, with cortisone, it is not unreasonable to believe that the patient is not as badly damaged and is more capable of healing than is the child with persisting proteinuria, who has seemingly suffered a glomerular injury irreparable by cortisone. Possibly the early effects on proteinuria by cortisone permit us to guess more closely the ultimate prognosis of a child with nephrosis. Certainly we do not believe at present that cortisone removes the agent responsible for the disease. To illustrate this point, I wish to show a slide, which I just did not happen to have, but which I deliberately brought along.

This slide summarizes the status of patients who have been treated with adrenocortical active hormones and who have been under observation for one to four years. The clear area at the top of the slide includes those patients in remission, i. e., with no clinical or biochemical signs of nephrosis.

The stippled area below the clear area depicts in percentages patients with continued activity of the disease but with no evidences of deterioration of renal function other than proteinuria.

The lined area below this represents patients with progressive loss of renal function, and the black area at the bottom indicates deaths.

At the end of one year, about 25% of 71 patients are in remission. Approximately the same proportion of patients are in remission after two, three, and four years. Certainly a fixed uniform plan of maintenance therapy directed at all patients would subject these patients to needless overtreatment.

The patients in the stippled group, who at the end of four years constitute about 25% of the total patients, are those whose disease is still present but potentially reversible.

The lined area is a group of patients which we feel will end up in the black area of the dead.

It is our impression that hormonal therapy has improved the clinical status and added to the well-being of children with nephrosis, and possibly prolonged the lives of some. However, one must be cautious in ascribing any prolongation of life to the use of hormones; the increased interest and surveillance, the more thoughtful and conservative management, the use of antibotics in prophylaxis in childhood nephrosis are some of the other factors which are not without effect on prolongation of life. It is our feeling that we have reduced deaths from complications and possibly prolonged life, but that we have had little or no effect on the ultimate outcome of the nephrotic syndrome per se.

DR. ALBERT DORFMAN, Chicago: I want to congratulate Dr. Riley on this massive job. But I should like to raise a couple of questions, one of which Dr. Rapoport touched on.

First, as far as the statistical comparison of these indices is concerned, I am a little bit troubled about the validity of applying statistical tests to an arbitrary index consisting of different quantities, because the statistical tests used assume in their very theory that the quantities are equal and that the variation follows a normal distribution curve; and, if these are not even approximately fulfilled, I think it is dangerous to speak of probabilities.

On the mortality data, I think one is on safer ground statistically; but I think there are some other questions.

Dr. Riley spoke of the question of bias from one point of view, but I should wonder about whether there are not numerous other types of bias which come into this kind of selection and retrospective study.

For instance, I am not clear as to what happened to the patients who came into institutions who were too sick or who got hypertension very readily with hormones so that hormone therapy was not practical.

Finally, it would seem to me that one can only conclude, I think, as Dr. Rapoport has already implied, that there was a difference between these two periods; but one cannot conclude that the difference was due to hormones.

If one's patients' sedimentation rates rise twice a week, one sees these patients twice a week. This is different from what was being done in 1946, and, as a matter of fact, a control period is not exactly a control period, because I am quite sure, in these centers, all sorts of things were done to try to cure nephrosis, some of which we now probably think are almost silly and may have actually harmed the patients.

DR. WILFRID W. PAYNE, Watford, England: I am afraid we cannot claim anything like the numbers you have reported here. I am very impressed by this magnificent presentation of Dr. Riley's.

We have, however, one slight modification of the method of treatment. At first we used the short-term method, with practically the same results in the long run as all other ways of treatment. We then started on to the longer-term treatment, resembling the maintenance method but differing in some particulars.

As an additional guide to treatments we have used plasma paper electrophoresis, a relatively quick and simple method.

Like Dr. Rapoport, we find that the proteinuria will disappear usually within the first 12 to 18 days.

When you look at the electrophoretic picture of the plasma proteins, you always find an immediate alteration of the $\alpha_2\beta$ complex on starting treatment. This is followed by a slow increase in the albumin and the $\alpha_2\beta$ complex resolves, until about the 18th day. Then, about half the cases will go on improving even though they are passing albumin, which may later disappear or fall to 100 mg. or less.

In another group, the albuminuria persists, and the blood picture goes back toward the original pure nephrotic picture, although large doses of cortisone are still being given.

In the first group, we continue the cortisone treatment until their electrophoretic pattern becomes completely normal. We do not stop treatment until we have a normal picture, as in our experience this is the last of the various abnormalities to return to normal.

With the other group, one has the problem of what to do with next. The question I want to ask is about the value of repeated courses. If we give this group of patients a higher dose or repeat the course of cortisone they often only show the tremendous changes you get with giving too much cortisone.

So our tendency has been to let them have a holiday, free from treatment; then we treat them again. Sometimes it has worked and sometimes it has not. I was wondering whether anyone could give any information as to what would be a reasonable length of this holiday, and whether it makes any difference whether you change to corticotropin (ACTH) from cortisone.

DR. BENJAMIN KRAMER, Brooklyn: In the treatment of these cases we emphasize the importance of repeated blood pressure determinations. In patients who do not do well, the blood pressure under therapy has a tendency to rise and may reach a very dangerous level.

In prolonged therapy, we have given repeated courses until the blood chemistry was entirely normal, including the sedimentation rate, the plasma protein level, and the blood lipid pattern. The restoration of the serum gamma globulin deficiency may be delayed. With the establishment of a normal blood pattern, therapy is continued following a course similar to that described by Dr. Riley. With intermittent proteinuria, it is impossible to say when permanent cure has been achieved.

There is a certain element of danger in the use of cortisone and related compounds because of the tendency of these nephrotic children to develop infections. The masking effect of cortisone upon the clinical symptomology makes early diagnosis difficult.

DR. PAUL V. WOOLEY JR., Detroit: There is just one question I should like to ask Dr. Riley. Certainly, our experience seems to be more and more, as time goes on, that we are changing the cause of death, not necessarily decreasing it. I wonder what his experience has been with those who did not survive, as far as the immediate cause of death is concerned. Undoubtedly, we have many more in the 3- and 4-year-old category running around today; but we seem to be burying many more in the 7- and 8-year-old category, who die of hypertensive renal disease.

DR. CONRAD M. RILEY, New York: I was very interested to hear Dr. Rapoport's experience.

Just a word about the use of proteinuria as a guide for treatment. I think, in general, it probably parallels the sedimentation rate as a useful tool; but there are individual cases every now and then who, despite their clinical well-being, continue to show heavy proteinuria. These children, in my experience at least, are subject to relapse of edema without detectable change in the degree of proteinuria; most of the time such relapses are associated with a rising sedimentation rate. If we can keep the sedimentation rate in those patients normal by treatment when they start to rise—this is an impression from only nine months' experience—it seems we can avoid such relapses.

Dr. Dorfman's remarks about the validity of any retrospective statistical studies, I think, are wholly justified. I can only say we have labored valiantly for a long period to get at the things he has mentioned, but it still remains a retrospective study.

The question he raised about what is happening to patients too sick to treat I hope we answered by comparing the patients according to the calendar year of onset instead of according to the type of treatment used.

Both Dr. Rapoport and Dr. Dorfman raised another question; whether seeing the patient more frequently has any therapeutic value. I do not personally feel that what we are able to do without hormones to the patient in frequent visits makes him any better off. I do not know whether that is enough of an answer.

Dr. Payne's following of paper electrophoresis is interesting. We have recently been doing it, along with our sedimentation rate, and, in a rough way, they very much parallel each other. I think we are probably going toward the same goal in using these two different techniques.

Dr. Kramer's remarks on general precautions about the use of these hormones, I think, are well taken. Certainly, they are not playthings which should be used too liberally.

In our experience, Dr. Wooley, the type of death up to the present time, I would say, has been the same kind of not too easily explainable death nephrotics have.

I have grave suspicions that the ones we are carrying along (I like to think holding in a somewhat arrested, although not wholly arrested, state) will eventually go on to chronic renal

failure, with a hypertensive phase; but, up to the present, this has not happened, and one can only hope.

Continuous Polarographic Measurement of Oxygen Tension in Whole Blood. Dr. Samuel Kaplan, Cincinnati, Dr. Leland C. Clark Jr., Yellow Springs, Dr. Edward C. Matthews, and Dr. Melville I. Singer, Cincinnati.

The method of polarography for the determination of oxygen tension depends on the following reaction which occurs at a platinum or gold-plated platinum surface maintained at —0.7 volts:

$$2H^{+}+O+2e \rightarrow H_2O$$

Although this method has been used for the determination of oxygen tension of pure electrolyte solutions or blood-free tissue preparations, the direct contact of red blood cells with the cathode interferes with the reduction of oxygen at this site. We have found that if the cathode is covered with cellophane, the red blood cell effect is obviated but diffusion of oxygen to the cathode surface continues.

The apparatus consists of a silver chloride anode and a gold-plated platinum cellophane-covered cathode. These electrodes are mounted in a plastic anerobic cell with an internal stirring device and having a volume of less than 1.5 ml. Construction of this appartus is such that a continuous but slow flow of blood through the cell is possible. The current which flows as a result of electrolysis is measured through a suitable circuit by a continuously recording galvanometer. After calibration of the cathode, direct measurement of blood oxygen tensions are made.

Results obtained by the continuous recording of the oxygen tension of arterial blood will be demonstrated. Also the prompt variation of the oxygen tension of arterial blood that occurs after breathing of various gas substances will be shown. The apparatus described above has been used to measure oxygen tension of urine which may reflect the variations of tissue oxygen tension. The significance of this study with respect to the effects of oxygen therapy in premature infants and older children will be discussed.

DISCUSSION

Dr. Bruce D. Graham, Ann Arbor, Mich.: I should like to congratulate the authors. They have succeeded where many others have failed, I think. We have struggled in this direction with electrodes and have succeeded only in establishing what we think is a worthwhile and successful method of determining plasma oxygen tensions.

I think they here are reaching in a long way on a certain concept, which we should consider more when we think about oxygen; which is, as the speaker has intimated, that when we consider oxygen supply, the volume per cent of oxygen which is contributed by the plasma is not much compared to the volume per cent carried by arterial blood, but it amounts to a considerable perecentage when we think in terms of an atrioventricular difference. I wonder if Dr. Kaplan would have anything to say about that.

Also, I should like to ask if you have made any simultaneous arterial and venous sampling.

We noted one thing when we were sampling venous blood from adults and also again when we were sampling that from normal newborn and premature infants. That was a rather consistent finding that we obtained no venous overflow, if you will, of oxygen when 40% oxygen was administered to premature infants but did see this with normal newborn infants and with our adult controls.

Dr. Clement A. Smith, Boston: This may well be a field where a lot of us would like to discuss but are not quite brave enough to ask questions which may strike Dr. Kaplan as a little silly.

I should like perhaps for the rest of us to ask him why the oxygen tension in such areas as the bladder urine or the kidney pelvis remains as low as it does. I can see why, with active metabolism going on, the brain might never get above a certain oxygen level, even though a large amout of arterial blood was reaching it at a tension which, one would think, would tend gradually to raise the local tension higher than was found.

But the urine is not metabolizing; it is just lying there, and its oxygen tension ought ultimately, I should think, to come into some sort of equilibrium with that of the blood supplying that area. Shouldn't this tension be higher?

Any further explanation of the differences between these various tissues would be most interesting.

DR. C. KENNEDY, Philadelphia: I just want to add that, recently, it has been shown that there is a considerable variability in the local circulation to the brain. Differences may be as much as fourfold or fivefold, depending on the location under consideration, and therefore, I think we would have to have several places studied before we could assume that the mean oxygen tensions in the brain were being given in a study of this kind.

DR. SAMUEL KAPLAN, Cincinnati: I should agree wholeheartedly with Dr. Graham that, in the studies of the effects of breathing high contents of oxygen, it is absolutely essential that we do oxygen tensions rather than oxygen saturations.

In reply to a question of his, whether we studied simultaneous arterial and venous oxygen tensions, we have not done that in this study itself.

In reply to Dr. Smith, I tried to indicate in the paper that the urine which we measured was, in fact, urine taken from the pelvis of the kidney. We did this specifically because we suspected, as he does, that perhaps urine lying around in the bladder might get the same tension as that obtained from the surrounding blood supply in the bladder.

Why this urine oxygen tension is so low is an extreme mystery. We have some pilot experiments which would suggest to us that, when we place a catheter in the kidney substance itself, we cannot get any response at all to oxygen administration; or perhaps I should not be as conservative as that, and say that the rise we get is very, very small.

However, in other tissues we have studied, they have all behaved more or less as the brain does.

I should like to thank Dr. Kennedy for reminding us that different parts of the brain have different blood supplies. I should like to mention to him that the cathodes which we used in these animals were all planted in the parietal lobes of the brain; that the cathodes were in position for approximately 7 to 10 days before any readings were obtained, and that daily continuous readings were obtained after that. With a cathode in this position, we can get duplicable results from many hours of continuous recording for many days after the cathode has been stabilized.

Physiologic Observations in Neonatal Respiratory Distress. DR. C. D. COOK, Boston, DR. P. KARLBERG, Stockholm, R. B. CHERRY, M.A., Boston, DR. D. O'BRIEN, London, DR. J. M. SUTHERLAND, DR. S. SEGAL, and DR. C. A. SMITH, Boston.

The disturbances of pulmonary function and the associated physiologic adjustments during neonatal respiratory distress have been investigated in 39 infants. Most of these infants presented the characteristic features of the hyaline membrane syndrome. Studies included measurements of simple ventilatory function (minute volume, rate, and tidal volume) and ventilatory efficiency (effective alveolar ventilation, functional dead space, and blood pCO_2). Functional residual capacity was determined by one of us (P. K.) in three infants with neonatal respiratory distress. In addition, measurements of intraesophageal pressure changes (as indices of intrathoracic pressure differences) during the respiration of 17 of the infants allowed calculation of the work of respiration and a description of the alterations in mechanical properties of the sick infant's lung. Although all the techniques were not applied to every infant, and some to relatively few, the results were sufficiently consistent to justify a description of the physiology of this syndrome.

These studies, which were correlated with clinical and roentgenological observations and compared to similar studies in normal infants, show that neonatal respiratory distress results in a decreased functional residual capacity (mean=—45%) and an increased functional dead space (+70%). Apparently in response to these handicaps, minute volume is increased (+75%), primarily as a result of a rise (+90%) in respiratory rate. Tidal volumes are comparable to those of normal infants. That the physiologic adjustments are incomplete is indicated by cyanosis in air, reduction in effective alveolar ventilation, and an increase in the blood pCO_2.

The abnormally large functional dead space is presumably due to (*a*) changes in pulmonary gaseous diffusion, (*b*) incomplete ventilation of portions of the lung, or (*c*) abnormalities in pulmonary circulation, or, more likely, to all three of these factors. In any case, dead space measurements indicate that only 30% of each respiration is exchanged with blood in the sick infant. This is in contrast to 70% exchange in the recovered or normal infant. Obviously, survival depends at least in part upon the degree of adjustment to the dead-space change.

The pressure-volume studies show a marked decrease in the distensibility of the lung and consequently a marked increase in the negative pressures necessary to attain approximately normal tidal volumes. This strikingly decreased distensibility presumably is the basis for the reduction in the functional residual capacity, and it is certainly, together with the increased minute volume, related to the large energy expenditure (+400%) for respiration in these sick infants.

Conclusions.—With proper care quantitative measurements of pulmonary function and mechanics of respiration may be made in newborn infants with respiratory distress. Such studies suggest that abnormalities contributing to an increased functional dead space are important in the pathophysiology of this condition. Cyanosis and elevated pCO_2 indicate that the infant's adjustment is often incomplete. The decreased distensibility of the lung and the consequent greatly increased work of respiration measured in these studies are undoubtedly limiting factors in adjustment and survival. Thus, therapeutic procedures should rationally be aimed at decreasing functional dead space and respiratory work, and their effects may be evaluated by techniques described.

DISCUSSION

DR. BERNARD SCHLESINGER, London, England: I was very interested in this paper; the question of the hyaline membrane has attracted us all, and there is still much doubt about its cause.

We at University College Hospital have been interested in one group which have the typical clinical picture but not the postmortem changes usually associated with this disease.

We believe that some of these cases may be due to cardiac failure caused by depression of the infant's cardiac or respiratory center from obstetric narcotics or by edema of the brain following birth trauma, and we have some evidence in support of this.

I was therefore interested in the second x-ray which Dr. Cook showed us, in which I thought the heart was larger than normal at the height of the infant's symptoms and reverted to normal when he recovered.

This has some clinical significance, because, in those cases in which cardiac failure can be established, we have been using digoxin and have put such premature infants into a state of low metabolic rate by not heating them. In several cases by this method we have obtained remarkable recoveries.

DR. CHARLES D. COOK, Boston: I should like to thank Dr. Schlesinger for his remarks. Our experience is similar to his, that is, not every infant dying of respiratory distress has had hyaline membranes on microscopic section. Therefore, we have tended to use the more general term "neonatal respiratory distress" to classify these infants. We too have found by x-ray that in a good many cases of respiratory distress the heart is enlarged. Particularly at the suggestion of Dr. David Gitlin, it is planned in the future to investigate cardiac failure as a possible etiologic factor in this syndrome.

The Effect of Reserpine (Serpasil) and Its Combination with Hydralazine (Apresoline) on Blood Pressure and Renal Hemodynamics During the Hypertensive Phase of Acute Nephritis. DR. JAMES N. ETTELDORF and DR. J. D. SMITH, Memphis.

Previous investigations by McCrory and Rapaport as well as our observations revealed that the use of hydralazine (Apresoline) during the hypertensive phase of acute nephritis resulted in a decrease in renal functions (glomerular filtration rate, effective renal plasma flow and filtration fraction). Nevertheless, in view of the temporary nature of these alterations, we have recommended its use under certain conditions when serious complications such as encephalopathy and cardiac failure are present.

Because of reported therapeutic advantages from a combination of reserpine and hydralazine, we have conducted studies in an effort to evaluate this combination in hypertensive nephritic children.

Reserpine alone when given in doses of 0.07 mg. per kilogram of body weight intramuscularly resulted in a gradual and moderate depression of the blood pressure with no alteration in the glomerular filtration rate or renal plasma flow and a slight decrease in urine flow. The administration of 0.1 to 0.15 mg. per kilogram of body weight of hydralazine (one-sixth to one-third the previously recommended dose of hydralazine alone) in combination with reserpine resulted in a rapid and prolonged hypotensive response. There was a slight increase in renal plasma

flow and no change or a slight decrease in glomerular filtration rate; the filtration fraction remained within the limits of normal, and the urinary flow decreased during the clearance periods.

In seven patients a single dose of this combination resulted in a sustained return to normotensive states; in six additional patients the duration of the hypotensive response ranged from 10 to 72 hours.

These observations indicate that a combination of reserpine and hydralazine in the above dosages may be the treatment of choice in the management of hypertension in children with nephritis.

DISCUSSION

DR. WALLACE W. MCCRORY, Philadelphia: I want to congratulate the authors for a very interesting and important clinical study. The management of hypertension in children with acute nephritis is still a challenging problem. There are obvious drawbacks to the use of magnesium sulfate in children. It may be of interest to hear our experience using reserpine alone. Our regimen of treatment has been slightly different than that reported here. We have begun therapy in our patients by an intravenous injection, using 0.05γ per kilogram of body weight. This dosage has usually produced obvious vasodilatation and slight falls in blood pressure in the range of 10 mm. of mercury but seldom significant falls in hypertension. The patients have symptomatically been improved, and on continuation of reserpine by the oral route we have seen no further elevation in blood pressure and the subsequent course has been uneventful. The agent then appears to be of some promise, though in the dosage we have used it has not produced marked falls in blood pressure. One point I should like to make concerns the effective dosage of hydralazine. The dosage we previously found effective for parenterally administered hydralazine was 0.2 to 0.25 mg. per kilogram of body weight. As reported by the authors, they observe a good hypotensive effect with half this amount. It is of interest to see that they did not get consistent marked falls in glomerular filtration rate at this lower dosage. I should like to have some further information concerning other measures employed in the management of the patients reported here. All of the subjects seemed to show disappearance of hypertension in periods of three to five or seven days. This is quite in keeping with the usual course of uncomplicated hypertension in acute nephritis in children. Was there any dietary restriction of salt employed in the management of these children, and were they receiving any other drugs?

DR. C. W. DAESCHNER, Houston, Texas: We have been interested in hypertension of acute nephritis, and particularly in the therapeutic value of some of the newer hypertensive drugs in its management. For the past 18 months, we have limited our observations to parenteral reserpine. We have used a considerably higher dose than Dr. Etteldorf, usually in range of 100-150γ per kilogram of body weight. Initially, we used smaller doses with quite variable response, but as the dose was gradually increased, the hypotensive response was more consistent and seemed to be rather closely related to the dose. Using the 100 to 150γ per kilogram dose, we have obtained rather consistent responses. We have now given about 65 individual doses to some 36 hypertensive acute nephritics, and at least 85% showed a significant hypotensive response (fall in mean blood pressure of 20 mm. Hg or more).

One interesting thing we noticed, which Dr. Etteldorf commented on briefly, was that, in two patients in whom we were doing renal studies, there was a marked increase in the rate of urine flow in association with the fall in blood pressure, and, in a number of others, we noticed a tendency to diuresis by the time the patient had returned to the ward. This is particularly interesting in light of the recent information in the French literature, which suggests that the rauwolfia alkaloids have a diuretic action under some circumstances.

DR. JAMES N. ETTELDORF [In Closing]: I wish to thank the discussants.

With reference to Dr. McCrory's question concerning other features in the management of these patients, we did not restrict salt; salt shakers are not permitted on any of our trays. We unfortunately did not have enough private rooms on the charity service, and, therefore, a majority of these patients were placed in the wards. Other facets of the treatment included bed rest, penicillin therapy, and observation.

With reference to Dr. Daeschner's comments, I think they indicate, then, that reserpine by itself may be much more effective than our results indicate. I should suggest, as a plan of therapy, that the patients be tried on reserpine alone. If a good response is obtained, then nothing else

need be given. If the blood pressure is elevating or the course of the patient is not satisfactory, hydralazine may be added. Again, if the encephalography and/or cardiac failure are present, I should give the two agents simultaneously.

Ventricular Septal Defect in Infants and Children (Results of Direct Closure in Twenty-Five Patients). Dr. Paul Adams Jr., Dr. Brian Kiely, Dr. Morley Cohen, and Dr. C. Walton Lillehei, Minneapolis.

The purpose of this paper is to review the clinical syndrome of young patients with ventricular septal defect of a severe grade, indicating need for closure. The results of surgery in the first 25 cases performed by the method of controlled cross circulation will be presented.

The 25 patients selected for this procedure had histories of repeated severe respiratory infections requiring hospitalization. Their rate of growth was severely retarded in most instances.

Physical examination revealed the characteristic thrill and loud murmur along the left sternal border. The pulmonary second sound was accentuated.

The ECG showed normal or right-axis deviation in most cases, left axis in only two patients. Right ventricular hypertrophy alone on the precordial leads was the commonest finding (many showing the RsR′ pattern commonly associated with atrial septal defect). About one-third of the patients showed combined right and left hypertrophy, and only a few showed isolated left ventricular hypertrophy. The roentgenograms showed cardiomegaly in all; increased pulmonary artery segment, increased pulmonary vascular markings, and left atrial enlargement were uniformly present.

On preoperative catheterization, all but one patient showed a significantly higher O_2 content in the right ventricle then in the right atrium. All patients showed a pulmonary hypertension of marked degree, usually closely approaching the systemic pressure. Only one patient showed systemic arterial desaturation; this patient survived closure of the defect. Serial heart catheterizations before operation on several patients showed more or less rapid progression of pulmonary hypertension over the span of years.

A review of the surgery reveals that 18 of 25 patients survived; 7 died at the time of surgery or within a few weeks following surgery, a "salvage rate" of approximately 70%. Of the last 11 cases there has been only one fatality, a "salvage rate" of 90%. There was no mortality among the donors, although there was one serious complication in the early cases.

There was a remarkable increase in rate of growth in those operated cases who were grossly undersized and who have been followed over six months. The thrill and loud murmur have disappeared in those surviving except for one case. Almost all surviving patients show a complete right bundle-branch block on the ECG. Three patients who have been catheterized now show absence of left-to-right shunt. Two of these, both under one year of age, show decreased pulmonary hypertension.

Several patients showed a syndrome of transient right heart failure about three weeks following cardiotomy, which responded to medical therapy. Pathology of small arterioles of the pulmonary bed and its significance will be reviewed.

DISCUSSION

Dr. Helen B. Taussig, Baltimore: Dr. Adams, we all congratulate you on the brilliance of open cardiac surgery; it is a very brilliant procedure. It is tackling a group of malformations which I believe most of the surgeons feel cannot be done by closed technique.

The serious question, of course, concerns the use of donors. I was delighted to hear you say you are now using artificial oxygenation methods. I hope that, in your discussion, you will elaborate on that point and tell us whether you have entirely changed to or are working on the perfection of the new technique, because, to my mind, it is a very serious drawback to open cardiac surgery to take any risk with either parent in an effort to save the child's life. Usually it is the breadwinner, or it is the mother who is caring for the family, whose life is risked.

To my mind, even if it is a one-in-a-hundred chance, it is a very serious thing if you lose the donor. For that reason, I have been against the procedure; and I think most of the surgeons feel that the ultimate aim is to get away from using a donor.

The other point I should like to emphasize—as did Dr. Adams himself—is that in discussing methods for the closure of septal defects, it seems to me that the constant aim of medicine and surgery should be the simplest method which would give us the highest degree of success. If you

can have a pretty good operation which will give you a pretty good result, I am very doubtful of the wisdom of using a more elaborate technique which has risk inherent in itself in order to obtain perfection until you have completely ironed out the wrinkles in the new procedure.

Therefore I feel that open cardiac surgery should be used only when the patients are in serious difficulty and when there is no other method by which they can be helped.

Finally let me reiterate that I certainly hope we will not be forced to use either parent or anyone else as a donor in order to try to save the child's life.

DR. ALEXANDER NADAS, Boston: I should like to congratulate Dr. Adams for his very wonderful presentation.

I should like to know what his indications for operation on ventricular septal defects are. It is obviously a very touchy problem.

I think the growth chart, such as he has shown, is very interesting. At the same time, I think ventricular septal defects have the strange capacity of improving as the baby gets over the first 6- to 12-month period. In other words, although I do not know that you could duplicate exactly the development he has shown in a patient who had not been operated on, something closely resembling that may very well occur in an unoperated patient who does get over the very perilous period of the first few months of life.

The second point I should like to make is that I was very gratified by the fact that these defects were obviously closed, since the shunts, by postoperative catheterization, proved to be abolished. If we are operating on these patients to prevent development of increased resistances, possibly that can be accomplished by this procedure as well.

When it comes to the third point (that is, by closing the defects, you are abolishing already increased resistances), I am wondering if Dr. Adams has any answers as to whether this can be accomplished by this method.

DR. JOHN SAMPSON, San Francisco: I should like to ask Dr. Adams if he has found any correlation between the degree of pulmonary hypertension and those cases which exhibit the evidences of failure which he has shown in his series.

DR. PAUL ADAMS JR., Minneapolis: In answer to Dr. Taussig's question about artificial oxygenators, we too are looking for and would prefer artificial oxygenators if we could find one which was as effective as the method we have been using.

We have three separate oxygenators which we are using. One is merely a pooled reservoir of venous oxygenated blood, and that can be used in young infants where it is possible to get 10 donors at the time of surgery. In the first few cases, it was certainly encouraging.

The second preparation is the biological oxygenator (dog lung) developed by Dr. Campbell, and that, too, has been encouraging but has had somewhat less use.

The third method is a bubbling oxygenator developed by Dr. DeWal, and we are in the process of evaluating that.

I think it has been noticed from the material in the first slide that very few conclusions can be drawn from a few patients; so I cannot say that these methods will ultimately work. We are considering this present series as the "gold standard" to judge the results of any further improvements which may come along.

In answer to Dr. Nadas as to indications for surgery, that is a hard question to answer in a short time. However, that question is often decided by you and other pediatricians and cardiologists from around the country. We almost hate to see patients referred from other centers, because we know they are the worst ones you have in your practice. The patients selected for surgery have really all been terribly sick and severely handicapepd by the malformation.

There are many ways of determining the handicap a child has. They have all been handicapped by growth failure, by hospitalizations for months and months, and by respiratory infections. Clinical judgment that the child is not apt to survive long enough for improved techniques to be developed is an important consideration. The chances of the patient getting higher pulmonary pressures before we are sure of the safety of new techniques make us feel that we are justified in going ahead in some cases.

Incidentally, we have still kept our high standards of selection of patients, even though the surgeons can get better mortality figures when the patient is not as critical, because we do feel that, within the next few months or the next few years, we will have safer methods. So we are holding off as long as we can safely.

But I think our evidence points toward the fact that pulmonary resistance probably does not change. We have had only one patient in whom pulmonary resistance fell following surgery, and perhaps that is an error of measurement of physiological data.

On the other hand, I do feel that the resistance, as postulated from the severe medial hypertrophy seen under the microscope, is probably not as significant as we once thought it was.

Dr. Sampson asked if there was any correlation between the pulmonary artery pressures (and, I presume, resistances, too) in the three patients who showed the right heart failure syndrome.

There was no significant correlation; although those figures vary widely so that, even though there is some increase, we do not feel it is significant unless we have greater numbers, and I do not have any more.

The Incidence and Prognosis of Nephritis Associated with Anaphylactoid (Schönlein-Henoch) Purpura in Children. Dr. Thomas K. Oliver Jr. and Dr. Henry L. Barnett, New York.

Adults with nephritis associated with anaphylactoid purpura are reported to have a relatively poor prognosis. The prognosis in children with this condition forms the basis for this report.

Twenty-six children with anaphylactoid purpura have been seen at The New York Hospital-Cornell Medical Center in the 11-year period 1943-1954. The age at onset ranged from 11 months to 10 years, with a mean of 4.3 years. The ratio of males to females was approximately 2:1 (17/9).

The incidence of nephritis, using hematuria and/or proteinuria as the criteria, was 42% (11/26). The age range in this group was 2½ to 10 years, with a mean of 4.4 years. There were 7 females and 4 males. One patient had proteinuria alone; the remainder had both hematuria and proteinuria; none had azotemia, hypertension, cardiac failure, or encephalopathy. Without exception, the onset of nephritis was within the first weeks of the onset of the disease.

To evaluate the course of the kidney disease in the patients with nephritis, tests of renal function (Addis counts, urea clearances, and the measurements of serum protein, albumin, globulin, and cholesterol) have been performed in all of the patients within the last six months and in 8 of 11 of the children repeatedly from the onset of the disease. One patient has been observed for only six months; the remaining ten have been followed for more than one and one-half years.

Three of eleven children still have symptoms: one has periodic gross hematuria, the other two have skin lesions and/or arthralgia. In all except the latter two physical examinations are entirely normal, and the blood pressure is normal in all. Addis tests are normal in all except three (two of the above), and in one of these there is only slight proteinuria. The return of the Addis count to normal was slower than is usually seen in patients with acute glomerular nephritis extending over one year in three of six patients where this time was known and being greater than four years three months in one. Transient hypoalbuminemia and/or hypercholesterolemia, which are rarely observed in acute glomerular nephritis, occurred within the first six weeks of active nephritis in three of the patients. In none of the 11 children was a reduced urea clearance observed. Corticotropin (ACTH) or cortisone has been used in six patients and, as reported by others, has not influenced the course of the disease.

Similar observations have been made in six children with anaphylactoid purpura but without nephritis at the onset. The results indicate that nephritis does not emerge as a late sequelae to anaphylactoid purpura.

Conclusions.—Renal involvement occurs in approximately one-half of children with anaphylactoid purpura. The uniformly favorable course in a group of 11 children with nephritis suggests that the prognosis of nephritis associated with anaphylactoid purpura is better in children than in adults.

DISCUSSION

Dr. Louis K. Diamond, Boston: I should like to add some supporting evidence to the statistical material presented by Dr. Oliver and to ask some questions based on the review carried out in our clinic by Dr. Howell and myself.

We reviewed some 75 cases over a period of five years, ending three years ago, and have had the opportunity to follow up many of these patients for three to seven years, or thereabout, after the acute phase.

In support of what Dr. Oliver has presented, we find too that the incidence of these symptoms is higher in the younger child than is acute glomerular nephritis in the young; but we have not

seen quite as high a percentage of symptoms of nephritis in the acute stages, in that only 18 of our 74 (roughly, a quarter) had evidences of acute hemorrhage or proteinuria while they were under observation on the wards.

Of these 18, however, we were able to follow some 17 by return outpatient visits, 1 having died of subacute glomerular nephritis with nephrosis. In contrast, as a control to this group, we had 25 children who had never had any manifestations of proteinuria, as far as we knew, while in the hospital.

In following these, we found (much to our surprise) that of the control group of 25 some 15 on reexamination had either altered urea clearance or an abnormal Addis count of much the same proportions as Dr. Oliver mentions, and of the 11 who had had nephritis 6 had altered Addis counts and 2 had very definitely abnormal urea clearance and still continue to have it. Also, two others had residual hypertension, suggesting that there was serious kidney impairment.

The condition is not quite as benign in the acute stage as seen by us as Dr. Oliver mentioned, in that we have had two deaths, one with renal failure and the other with acute intussusception following severe hemorrhage and edema of the bowel.

It would seem that, if one took these follow-up studies of kidney function as seriously as they seem to imply—and these have been reviewed by Dr. Metcalf in our kidney laboratory—a considerable number of these patients, three to seven years later, still have trouble.

One question I should like to ask Dr. Oliver (and a point which has been very striking in our series) is on the very marked increase in incidence of this disease, in that previous to 1947 we were seeing on an average of five cases a year in the wards; we may have seen an equal number of milder manifestations in the outpatient clinic. In the five-year period beginning 1947, we have had about 15 patients a year in the ward service, and, since 1952, this high incidence continues, in that we are seeing 15 or 20 new cases every year.

Since many of our patients continue to have purpura or joint manifestations for a considerable time, we have felt that the exacerbations of the purpuric manifestations are signs of the continued activity rather than a relapse in a process which had healed in the meantime.

From the data which Dr. Howell has collected, we should feel that anaphylactoid purpura represents a generalized vascular disturbance, and this, of course, is confirmed by skin biopsy on many of these patients. Although many of them fail to show evidence of nephritis while being studied in the acute stage, it is possible that, if there is better observation or a more thorough study at a later time, it will show a higher incidence than the series reported by Dr. Oliver.

Finally, the prognosis may not be quite as good as we had originally thought, in that quite a few of these children continue to have some evidence of kidney impairment.

DR. MITCHELL I. RUBIN, Buffalo: I think there must be a wide pattern in which renal involvement occurs in so-called allergic purpura.

We have had experience similar to Dr. Diamond's in increase in incidence of allergic purpura over the past several years. During a period of six years we have had 65 patients with this disease.

Of these 65 patients, 9 had gross hematuria; 1 of them had as many as 10 episodes of gross hematuria. The longest interval between attacks of hematuria in any patient we have observed is a little over a year; in other words, the prognosis cannot be established too quickly.

Our experience with these patients is somewhat in variance with the data presented by the speaker; we have had some serious complications, in fact, one patient last week died of his disease, having developed a nephrotic syndrome. It is the first such experience we have had in a patient with this disease. In the early stages of his illnes he exhibited the ordinary hematuria which we had seen several times before in purpura. However, this patient developed progressive renal failure and finally the nephrotic picture.

In about 70% of our total patients we recovered hemolytic streptococci from the nasopharynx during their first attack. I do not know the significance of this latter finding in the etiology of this disease, the streptococci were not typed and antibody studies were not made. However, in subsequent attacks infection oftentimes could not be demonstrated at all. One wonders whether the recurrences may be an expression of an antibody chain reaction such as was suggested by Dr. Najjar in an eariler paper at this meeting.

In some ways the disease is not too dissimilar from ordinary acute nephritis; the majority of our nine children having gross hematuria (20% of our patients with purpura had hematuria, 9 children had gross hematuria) had an elevated blood urea nitrogen. The glomerular filtration

rate in those patients so studied was reduced early and later returned to normal. It may be reduced in one episode of hematuria and remain normal in another. There is quite a variable picture of both clinical and functional expression in this disease.

I feel some concern about the ultimate prognosis of the patients with recurrent episodes of renal involvement.

DR. GEORGE M. KOMROWER, Manchester, England: Four quick observations.

First, there certainly seems to have been a higher incidence of this condition in England over the past three or four years.

Second, the relationship to streptococcal disease. In the autumn of 1953 and 1954, we experienced an epidemic of mild streptococcal infection, certainly in my part of England, and, as a result, we had an increased incidence of rheumatic fever, acute nephritis, and anaphylactoid purpura. We felt that there was certainly some superficial evidence that this condition was related to Streptococcus.

Third, we have certainly had appreciable residual renal damage as a result of this condition, so much so that we are always concerned when a child with anaphylactoid purpura develops hematuria.

Fourth, we have found that cortisone is of some value, particularly in the cases where the abdominal symptoms are extremely severe.

DR. RALPH J. WEDGWOOD, Cleveland: Dr. Oliver mentioned that Dr. Klaus and I also had a series of such patients in the abstracts of these meetings. We studied 26 patients and found 10 with what we would consider to be nephritis. This nephritis, on follow-up, was characterized mainly by hematuria. It has remained remarkably consistent for the period during which we have been following these children since calling them back for study.

We have certain differences with Dr. Oliver and Dr. Barnett. First of all, the age at onset of the purpura in our patients who developed nephritis was always, and this is statistically significant, higher than that of the group which did not have nephritis on follow-up. Secondly, six of our children now have abnormal urine more than five years after the onset of their disease, and three more than three years since their purpura appeared. During this follow-up period they have been without any other manifestation of their original purpuric disease. This suggests to us that the hematuria seen now is a sequel to, rather than only a manifestation of, the acute episode of purpura.

Finally, we do not feel that the prognosis can be considered uniformly favorable. If our children had had clearing of their urine in one year we too would have felt relieved. But our children, who still have hematuria some five, six, seven, or eight years after the onset of their acute disease, constitute in our minds a much more serious problem, and we consider that the prognosis must, at least, be guarded. We prefer to regard them as latent nephritics. There is good historical precedent for this point of view, as Dr. Oliver has already pointed out, and in addition the available descriptions of the histologic lesions of the disease lend considerable pathologic backing.

Eight of our children with this nephritis have now passed into the adult age group, and at the time that they passed into this group they had no personal awareness of the fact that they had abnormal urine. I should therefor enjoy hearing Dr. Oliver comment on a little speculation. We wonder whether this disease might constitute one of the origins of chronic renal disease of "unknown etiology" in adult patients which we, as pediatricians, believe rarely follows acute glomerulonephritis, and whether an episode of purpura in childhood could have passed unnoticed or unremembered, so that the etiology of the adult nephritis might have been obscured.

Then, finally, we wonder whether this disease, which has such a broad spectrum of manifestations and apparently, from the comments on Dr. Oliver's paper, such a broad spectrum of nephritis, could exist—and I apologize for this term—in a forme *fruste, sine* purpura, with nephritis alone as the only manifestation.

DR. CHARLES PRYLES, Boston: There is only one question I should like to ask Dr. Oliver, in view of the shortness of time. Has he been able to study the kidneys of any of his patients from the pathologic standpoint, and if he has, can he differentiate these kidneys from those of patients dying with acute or subacute glomerulonephritis associated with Group A beta hemolytic streptococci?

DR. CHARLES A. JANEWAY, Boston: It is worth calling attention to the fact that in addition to the evidence Dr. Oliver has given, there is another important difference between this disease and acute glomerulonephritis. One of the characteristic manifestations of acute glomerulonephritis

is a marked reduction in serum complement during the acute phase. On the other hand, in this type of nephritis, described by Dr. Oliver, almost universally investigators have found that the complement level is not at all reduced; if anything, as Dr. Wedgewood showed, it may be a little elevated, which again suggests that pathogenetically it is quite a different disease.

DR. THOMAS K. OLIVER JR., New York: Shortly after our arrival here, it became apparent that this disease had been studied by a number of individuals throughout this country and abroad. I am delighted that they were able to comment and that our experience, while not entirely similar, was not drastically different.

I should like to comment at the outset that we agree, as I tried to indicate by the experiences of Dr. Wedgwood and Dr. Gairdner, that this disease may well have a worse prognosis than the experience we had.

I should point out that one of the important features of the disease is that the Addis count may persist in being abnormal for prolonged periods, and this is not of itself necessarily to be construed as constituting a bad prognostic sign.

Dr. Diamond, Dr. Rubin, and Dr. Komrower all noted that there is an increased incidence in the last few years. This, too, has been our experience, and I cannot explain it.

Dr. Diamond commented on skin biopsies. We have done these in three cases, and they were normal in all.

We also looked in the nail beds of two patients with active purpura and found that their capillaries were entirely normal.

Dr. Rubin comments on a patient who died with the nephrotic syndrome. This, to my mind, is a unique experience and is not reported elsewhere.

We, too, agree that, in patients with recurrence, we did not see that many of them had any infection preceding.

We have not had the experience Dr. Komrower, of the value of cortisone in relieving the abdominal manifestations of this disease.

Dr. Wedgwood comments on the possibility that this represents a latent nephritis which will become chronic nephritis in adults. This simply has not been our experience, and I could not say anything more than that. We have not seen any children who had this disease without the other manifestations of the Schönlein-Henoch syndrome. I think there is one report in the literature of a patient who had nephritis and then, one year later, had the appearance of the triad of symptoms. This, again, is not our experience.

Dr. Pryles asks if the pathology of our results was good. We have no data on renal biopsy.

Our experience with serum complements is as Dr. Janeway indicates, and, in the three or four pateints on whom these studies were performed, they were quite normal.

Spectrum and Specter of Pulmonary Hypertension in Patent Ductus Arteriosus. DR. EMMA LOU SAILORS, DR. RICHARD L. FOWLER, and DR. C. GORDON SELL, New Orleans.

Variations in pulmonary blood flow and pressure explain many disturbing symptoms, many otherwise confusing physical signs, and are of major diagnostic and prognostic importance in patients with patent ductus arteriosus. Laboratory elucidation has been sought by cardiac catheterization. Our patients (23 children) are divided into three groups, based on severity of pulmonary hypertension: 13 in whom pulmonary arterial and aortic pressures were nearly equal, 3 who had "typical" patent ductus with pulmonary arterial pressure normal or only slightly elevated, and an intermediate group. Age at catheterization ranged from 7 months to 12 years; only three patients were older than 7 years, and eight were under 2 years.

Seven complicating lesions were recognized in six patients, but the ductus was important in each. Surgical inspection revealed the ductus to be large in 15 children and small only in the "typical" group.

Calculated pulmonary blood flow roughly paralleled difference in pressure between the two circulations in those with large ducts. It varied from 0.8 of systemic flow (in a child with severe pulmonary hypertension) to 4.5 times systemic blood flow (in one who had moderate pulmonary hypertension); this correlation was absent when small ductal size provided a natural barrier to flow. An illustration of progression from moderate to severe pulmonary hypertension with concomitant decrease in left-to-right shunt is presented. Clinical histories and previous observations of the patients suggested an earlier phase of "flooded lungs" in patients with severe pulmonary hypertension.

The ultimate in pulmonary hypertension, reversal of flow—right-to-left shunting of unsaturated blood from main pulmonary artery into descending aorta—was demonstrated in four instances.

Characteristically, the physical findings in those children with severe pulmonary hypertension included extremely loud and split pulmonary second sound, absence of continuous murmur, and variability (even absence) of systolic murmur; growth retardation was striking. By contrast, children with more usual relationships, i. e., a large discrepancy, between pulmonary and systemic arterial pressures presented classical findings of patent ductus. Moderate to marked cardiac enlargement was found except when the ductus was small.

Electrocardiography most often indicated combined ventricular hypertrophy, except in children with small ducts; right hypertrophy was characteristic of those with pulmonary hypertension.

Surgical ligation was attended by 4 deaths among 10 operated upon in the presence of severe pulmonary hypertension; no other operative mortality has been encountered.

From observations in this report, several conclusions can be drawn: patent ductus arteriosus in children is frequently productive of severe pulmonary hypertension which may be progressive; reversal of flow can occur even in young infants. Pulmonary flow in the presence of severe pulmonary hypertension is usually only moderately increased; under these circumstances the clinical picture differed from that usually associated with patent ductus arteriosus.

DISCUSSION

DR. HELEN B. TAUSSIG, Baltimore: We have all been interested in the problem of pulmonary hypertension in patency of the ductus arteriosus. I think there are two distinct entities. One is patency of the ductus arteriosus in which there is pulmonary hypertension, and the other is pulmonary hypertension when there is persistent patency of the ductus.

I believe you were speaking entirely, or almost entirely, of the group in which patency of the ductus arteriosus was associated with pulmonary hypertension. There again, in an infant the pressure in the two circulations is more nearly equal; in this age group, pulmonary hypertension of some degree, I think, is the rule. The larger the ductus, the greater the flow of blood to the lungs, the slower is the pulmonary bed in opening up, the later the continuous murmur develops, and the more frequently you will find pulmonary hypertension. Indeed, you showed that in the severe group with a big heart there was pulmonary hypertension.

When the heart is small you do not expect to get pulmonary hypertension. With a small ductus and a small heart it is usual to have a balanced electrocardiogram, or with a large heart there may be evidence of what we call "combined" hypertrophy. Occasionally, in infants ,you will even see the two pressures so nearly equal that you may get slight shunt reversal; but overwhelmingly the direction of the shunt is from the aorta to the pulmonary artery.

We have seen more and more pulmonary hypertension. Pulmonary hypertension may be primary or secondary to a cardiac malformation; under the latter circumstances, pulmonary hypertension occurs when systemic pressure is reflected to the right ventricle or when there is tremendous pulmonary flow. In contrast to this, primary pulmonary hypertension means that the abnormality lies in the lungs. We do not mean that it may not be secondary to an infection in the lungs, but we do mean that the heart itself is normally formed.

I personally think that we are going to find a wide variety of causes of primary pulmonary hypertension; I have seen primary pulmonary hypertension in all age groups, from infants to adults.

In this group, occasionally, the ductus may remain patent. This is the group in which there is the classical picture of a reversed flow of the blood through the ductus causing cyanosis of the feet, sometimes cyanosis of the left hand, and normal color of the right hand and head.

This group is usually characterized by a small heart and evidence of right ventricular hypertrophy in the electrocardiogram. The ductus in this group, I feel, is acting as an escape mechanism; it is preventing the pulmonary pressure from rising appreciably above systemic pressure. It is an escape mechanism, and consequently we feel that ligation of the ductus is contraindicated.

Finally, there is an additional group of malformations with reversal of flow due to the low pressure in the systemic circulation; that is a different problem.

In some of the older children with a patent ductus and pulmonary hypertension we are much influenced by the size of the heart and the height of the pressure in the pulmonary artery. If you

have a small heart and a high pressure in the pulmonary artery and evidence of great right-sided heart strain, I do not believe the hypertension is due to the large volume of blood to the lungs.

Some of those patients will have evidence of a left or right shunt upon cardiac catheterization. Maybe Dr. Sampson will have something to say about this group in a little while; we feel very hesitant about closure of the ductus in this group. I feel that pulmonary hypertension may even be congenital, or there may be some mild degree of pulmonary abnormality which is aggravated by intercurrent infections and gradually increases in severity, so that initially the flow of blood is from the aorta to the pulmonary artery, and later the pressure rises and the ductus is going to act as an escape mechanism.

In primary pulmonary hypertension one is struck by the fact that the heart is small and the ductus has remained patent, and yet the pulmonary pressure is high. I am quite sure you have seen some of those. You may like to comment on your experience in that line.

DR. PAUL R. LURIE, Indianapolis: I should like also to reclassify Dr. Sailors' first group, that with systemic pulmonary hypertension. Perhaps I can come at it from a little different direction and make it sound reasonable; I do not know.

We certainly agree that there are two general types in the group with systolic systemic pressure in the pulmonary tree: those with the large hearts and engorged lung fields, versus those with the compact, hypertrophied hearts, which have a large main pulmonary artery but small distal pulmonary arteries.

We can speculate, I think, that in the group with the small hearts the shunt has never been large; it has always been balanced, because of retention of the fetal pulmonary vascular resistance, as opposed to the type with a large heart, where the resistance has fallen and the shunt has at one time been very large then gradually, over varying periods of time, has been cut down again by the reaccumulation of pulmonary resistance.

The reason I should take this different approach from that of Dr. Taussig in classifying these two groups is that, usually, the ductus, to which she refers as an escape valve, is tremendous in the group with the small hearts, and, if all that is necessary is an escape valve, I do not think it needs to be that big.

DR. JOHN SAMPSON, San Francisco: I think this is a very critical situation, because all of us are confronted with the problem as to whether or not we are to operate on a patient with a patent ductus arteriousus, and that obviously is the direction in which the discussion has taken place.

It is a very strange situation; it seems to me that the so-called congenital pulmonary arterial defects which result in high resistance in the pulmonary arterial bed should be recognized as relatively so infrequent except in the presence of certain congenital diseases with left-to-right shunts, wherein they are more frequent.

We therefore, presumably, have two factors, the dynamics of which are fairly well recognized, the one which Dr. Taussig well points out, the congenital pulmonary arterial defects, and the one where the excessive pulmonary blood flow will increase this pulmonary hypertension. To define the type of case on the basis of the size of the heart certainly is an important clinical observation.

Our chief concern is whether we have sufficient evidence that the additional pulmonary blood flow is doing further damage by additional narrowing of the pulmonary arteries and the maintenance or advance of the pulmonary hypertension by the implements of flow.

On this supposition the existence of any amount of left-to-right shunt, as evidenced by increased oxygenation of the pulmonary arterial blood on catheterization of the pulmonary artery, would be an indication for ligation or section of the ductus. Difference of opinion is fairly well exhibited all over the world on the indications for severance of the ductus. Those who have lost cases with significant right-to-left shunts and a primary pulmonary hypertension on ligation of the ductus are very loathe to undertake the operation under these circumstances.

An occasional case, as has been reported by the group in Mexico who seem to have been brave in operating on some right-to-left shunts, results in some degree of improvement.

Insofar as you are driven into a corner by patients with pulmonary hypertension and right-to-left shunts dominantly who seem to be going down hill, and since at present there is nothing else you can do to better the situation, you may be impelled to ligate, in recognition of the risks. Future experience on the course of such cases may help to formulate the indications for operation.

DR. EMMA LOU SAILORS, New Orleans: As Dr. Taussig has indicated, probably most of our cases fell into that first group, in which the pulmonary hypertension was secondary to or a result of widely open patent ductus.

There was one patient, the first in our group, who was 12 years old and had reversal of flow and cyanosis in three extremities, in whom we, of course, could not document this condition, and the history was a bit suggestive that this situation might have attained all her life.

The clinical histories, although we could not go into them here, might suggest that there might have been an earlier stage of flooded lungs. There were two or three who did show a reduction from very large to moderate heart size. In our group of severe pulmonary hypertension you probably noticed that eight showed only moderate cardiac enlargement at the time studied. For of our patients showed shunts in both directions; and, in No. 6, of course, we showed a reduction in the shunt over a period of a year and a half.

As to the question of surgery, six of the first group did have surgery; one was a patient with a shunt in both directions, in which the left-to-right shunt was presumably a great deal larger at the time of ligation. She did very well, and died a month later. Of the others, one has considerable hypertension postoperatively. There were two in which there really was a satisfactory surgical result.

A Study of the Late Complications of Juvenile Diabetes in Approximately One Hundred Cases Using a "Free" Diet. DR. W. W. PAYNE, London, England.

For the first 10 years in our clinic strict weighed diets were used, but in 1936 experiments in "free" diets were started, and nearly all the patients had been transferred to "free diets" by 1940.

In this diet the child may eat as much as he likes of the simple foods used by his family, but meal times should always be regular and the intake of table sugar, jam, sweet cakes, and chocolate should be restricted, as was usual in the Victorian household of the past. With regard to diabetic control, a complete absence of all symptoms and normal growth were considered essential, and as far as possible, one dose of insulin a day was employed in a combination to obtain maximum freedom from glycosuria without hypoglycemic symptoms. Absence of significant ketonuria and blood sugar levels of less than 25 mg. per 100 cc. three hours after a meal were aimed at.

The cases were divided into three groups according to the degree of control achieved. They were examined for eye, kidney, vascular, and neurological involvement. In common with others we have found a well-marked correlation between the duration of diabetes and retinitis and a slight correlation between control and retinitis. There were very few cases of renal involvement or hypertension, and none showed neurological or peripheral vascular changes clinically.

In our experience, the majority of parents and children cooperated well when this liberal diet is used, and we found that the control obtained by the "free" diet was as good and often better than that with a restricted diet in those patients who were changed over from weighed diets in the late 1930's.

Comparison with reports of the outcome in similar groups of children treated by stricter methods of dieting in other clinics shows our over-all results to be no worse on the "free" diet, and probably somewhat better.

DISCUSSION

DR. GEORGE M. GUEST, Cincinnati: I should like to express my personal gratification on hearing Dr. Payne's report, which supports the practices currently followed in the Cincinnati Children's Hospital diabetic clinic. We adopted the so-called "free-diet" regimen around 1940, at first gradually, for a few patients, then for all. Let me note as did Dr. Payne that many of the children had already followed these practices without official permission at a time when they were supposedly following dietary prescriptions for measured diets.

Our instructions to parents and children are essentially like those of Dr. Payne, of Lichtenstein, and others who first talked of the free diet as distinguished from more strictly prescribed measured diets. In the group of diabetic children followed during the past 15 or more years, growth and development have been satisfactory as judged by standards applied to nondiabetic children.

We are all much concerned with questions regarding the late complications of diabetes mellitus. All agree that degenerative vascular disease is commoner in diabetics than in nondiabetics; but, despite many published statistics on the incidence of complications among different groups of diabetics, classified by different standards describing their "control," let us admit

that basic knowledge of the etiology of these complications is woefully lacking. I should like to call attention to the exceptional examples not uncommonly noted among various groups of aging diabetic patients who started as juvenile diabetics. Some who presumably followed faithfully the precepts of a carefully prescribed diet and insulin control have developed retinopathy and renal disease early despite the best care. On the other hand, a few others whose regulation was poor or even careless by anyone's standards have remained free from recognizable degenerative lesions more than 30 years. I suggest that these exceptional cases merit the most attention in our search for basic factors that influence the development of the late complications of diabetes.

The British geneticist Harris suggested that diabetes is determined by multiple genetic factors. It may be that various degenerative lesions which complicate the course of diabetes may also be determined by separate familial traits. Those traits might be disclosed by close study of the exceptional cases to which I referred.

DR. DOUGLAS VERNON HUBBLE, Derby, England: Sir, I think this is a very important paper for those who are interested in the diabetic child.

I think, though, that the pediatrician should remember that this question of free and restricted carbohydrate diets for children is still a matter of acute controversy.

You have already heard that the English controversial methods are more robust than those practiced in this courteous climate, and when I extolled the virtues of the free diet in a meeting in England, Professor Dunlop told me, in the words of the great Canadian humorist, Stephen Leacock, that this was simply a "Moonbeam from the larger lunacy."

Nevertheless, I think that diets are, to some degree, irrelevant. I should not wish to be misinterpreted here; but I think that much more important than the question of diet is that of insulin. I believe that we should insure, as far as we can, that children have an adequate amount of insulin present in the metabolic pool throughout the 24 hours. This is now much more easily possible than it was 10 years ago.

I believe that this has important consequences for the diabetic, not only in the matter of assimilation of foodstuffs, but also in the maintenance of normal endocrine homeostasis, and I believe that, in a small group of children, things begin to go wrong if, in their endocrine status inadequate amounts of insulin are available by day and night. This is important not only in the prevention of complications but also in the prevention of abnormal states such as the Mauriac syndrome and hypopituitarism.

DR. RICHARD WAGNER, Boston: The problem discussed by Dr. Payne and by other workers in this field for quite a few years is still rather controversial. Both sides (those who advocate a strict diet and those who advocate a more liberal diet) present their points of view with the same enthusiasm. However, both sides offer good proof for their satisfactory results.

When we started to take care of juvenile diabetics in 1921, our diets were rather strict. This was natural at that time. But gradually we had to give in; occasionally, we were forced by the patients into a more liberal regimen and had to make a virtue out of necessity. However, I still believe that excessive overeating leads to disaster and repeated occurrences of acidosis and coma, particularly in boys at the age of puberty.

It is hard, as Dr. Guest just pointed out, to evaluate the incidence of complications only from the angle of diabetic control. The problem is rather complex in nature. Diabetes is not simply a carbohydrate-metabolism problem, hence, a state of hypoinsulinism comparable to other deficiency states.

I have seen both early occurrence of severe complications in patients with perfect control of diabetes and excellent compensation in habitual diet breakers.

So long as we do not fully understand the development of complications, we should emphasize at least the obvious advantages of adhering to a reasonable diet, with not too rigid restrictions. In the carbohydrate intake, we may be rather liberal, as long as the carbohydrates are given in a low-fat, i. e., a relatively low-Calory diet. Let us not forget that the low-Calory diet was the diet of choice in the preinsulin era and saved many lives up to the time of the discovery of insulin. Its advantage is still true today. It reduces the daily intake of insulin and protects the patient from repeated occurrence of insulin reactions.

DR. ROBERT L. JACKSON, Columbia, Mo.: The introduction of the term "free diet" has resulted in considerable confusion, since the term is interpreted differently by different people. In my opinion, it is not desirable to permit any child, diabetic or otherwise, to eat without supervision and direction. A large percentage of children are receiving inadequate diets because of excessive intakes of unessential foods. This type of eating pattern should be discouraged

for all children. The only difference in the dietary program for the diabetic as compared to the nondiabetic child, according to our regimen, is that we plan the diet so that he has a predictable caloric intake given in the proper relationship to the type and amount of insulin that has been administered to avoid glycosuria and insulin reactions. We also have pointed out repeatedly that importance of adjusting the food intake to compensate for variations in physical activity.

In 1948, we reported data which show that both the degree of control and the duration of disease are significant factors in the development of degenerative changes in juvenile diabetes. We have continued our observations, and the data on our patients analyzed to January, 1955, continue to show a high correlation between the incidence and severity of degenerative changes and the degree of control of the disease.

DR. WILFRID W. PAYNE, London, England: I think Dr. Guest and I see so closely eye to eye that I can only thank him for adding many things which time did not allow me to say.

The relationship between the degree of control and the incidence of complications is only a relatively small one, but, though small, it is undoubtedly a real factor. As we have no idea at the moment how to affect the incidence of complications if we think there is say a 20% betterment when the control is good, then control is worth while.

I do not think there is a lot of difference between all the speakers in the belief that control is necessary; but people are continuously mixing up diet and control. They say they have their cases on a strict diet and therefore their control is better.

That is not the point. The point is, can you control your patients better on a strict diet or on a free diet? With which do you get a better general level of blood sugar, freedom of complications of hyperglycemia and hypoglycemia?

Dr. Wagner says he gets much coma and hyperglycemia in the adolescent boy. I do not get that. It is practically unknown in my clinic. I get it in the adolescent girl in the premenstrual period, but I have had less on the free diet. I think if one can control equally as well on a strict diet or a free diet, it is better to use a free diet.

Metabolic Abnormalities in Hypophosphatasia. DR. D. FRASER and DR. E. R. YENDT, Toronto, Canada.

In 1948, Rathbun reported from this hospital the first example of a metabolic disorder which he designated hypophosphatasia. His article and the nine which have appeared subsequently suggest that the essential features consist of defective calcification of bone matrix associated with alkaline phosphatase activity much below the normal range.

The present communication reports the clinical, biochemical, and histological findings in a baby girl with characteristic abnormalities in skull, long bones, and serum. We recorded in particular two aspects of the investigation which we believe are helpful in elucidating the pathogenesis of hypophosphatasia and which may be of interest in the study of bone metabolism in general.

We have shown that calcification took place in vitro in the cartilage of rachitic rats when slices of tibia were incubated at 37.5 C for 48 hours in the serum of the patient. On the other hand, it was impossible to produce demonstrable calcification in slices of the patient's costochondral junction incubated in the pooled serum of healthy growing children or in a synthetic calcifying medium. We present these experiments as evidence that defective calcification in hypophosphatasia results from an abnormality in the bone matrix—a disturbance which we believe from other evidence commences about the time of birth.

The presence in our patient of metabolic bone disease prompted us to study the urinary amino acid pattern by paper partition chromatography. In addition to the usual amino acids we repeatedly found a ninhydrin-positive substance similar in every property so far tested to aminoethyl phosphoric ester ($NH_2.CH_2.CH_2.O.PO\ [OH]_2$); this substance has also been referred to as phosphoryl ethanolamine. The material was also present in the plasma, which would suggest some nonrenal metabolic disturbance as its source. The substance has not been detected in recent urine samples.

The parents of the patient are healthy and have no clinical evidence of skeletal abnormalities. They both have levels of alkaline phosphatase activity considerably below the mean normal adult value, and both have low concentrations of the abnormal substance in the urine and plasma.

The ninhydrin-positive material has not been reported heretofore in urine or plasma of normal persons, and its relation to the normal and abnormal metabolism of bone warrants further investigation.

DISCUSSION

DR. BERNARD SCHLESINGER, London, England: We in London have been interested in this extraordinary syndrome and, with Luder and Bodian, have been studying three cases for some time. I should like to make three clinical comments.

First of all, Dr. Fraser's case apparently started after birth. I have seen an example which began antenatally. Here the intrauterine x-rays of an unborn sibling of a typical case belonging to Professor McCance and Dr. Gairdner showed the characteristic changes in the bones. So the condition can occur very early.

Secondly, a bad prognosis is likely if the age of onset is very early, particularly before birth, if renal involvement is severe and if the degree of phosphatase deficiency is gross.

The third point I should like to make is the danger of craniostenosis. In one of our cases which we have been able to follow up to the age of 2 years, a severe degree of papilledema developed, necessitating reconstruction surgery of the sutures.

I think this must always be borne in mind, because the prognosis as far as the bones are concerned may be quite good, and, if one does not keep an eye on the retinae, a child may recover but be left blind.

May I finally congratulate Dr. Fraser on presenting this case, because I think it is a most important condition, which opens up all sorts of possibilities.

DR. L. EMMETT HOLT JR., New York: I should like to raise a question as to whether there are incomplete forms of this condition. I have never had the opportunity of seeing a typical case of hypophosphatasia, but we have had the opportunity of studying a child with persistant rickets who had an unusually low phosphatase but none of the additional features which have been described with hypophosphatasia. I wonder if anyone else has seen partial forms of this disease.

DR. BRUCE CHOWN, Winnipeg, Man., Canada: Just for the record, I think I reported two of these children in 1936 (*Brit. J. Surg.* **23**:552-566, 1936). I did not give the condition from which they suffered, this name, of course; we owe that to John Rathbun.

These were sisters born about two years apart. In addition to congenital "rickets" and early nephritis they had one other thing which I am not sure has occurred in other of these children, curious nervous-system symptoms suggesting an autonomic type of epilepsy, in which they would get a fascinated look in their eyes, burst into terrific perspiration, utter curious high cries, refuse to feed for two or three minutes, then settle back into a normal state. Both died under a year.

DR. EDNA H. SOBEL, Boston: Dr. Fraser asked me to comment on genetics. I am still not sure that we can call this a genetically determined disorder, since the possibility of a toxic factor has not been eliminated entirely. I know of 11 affected children in 7 families. In three of the seven families there are unaffected siblings. The serum alkaline phosphatase activity of the parents is known in six families. In three instances, only one parent has low enzyme activity; in the other three families it is low in both parents. None of the parents have bone disease.

At first it seemed that there might be a correlation between a severe form of the disease (such as demonstrated by Dr. Fraser's patient) and the finding of deficient plasma enzyme activity in both parents. This relationship does not hold up completely, for a patient who has been studied in Boston recently, by many people, is severely affected but has one parent with normal plasma alkaline phosphatase activity.

It seems to me that what kills the seriously affected children in infancy may be their hypercalcemia and renal disease; it is very hard to know whether this is related to low alkaline phosphatase in the kidney itself, or whether it is secondary to the vitamin D therapy which is usually offered to a child who has bone disease. In the patient we studied, urinary calcium excretion was low, and hypercalcemia developed rapidly in response to 50,000 units of vitamin D daily. The tendency to hypercalcemia may be due to a combination of a skeleton which does not mineralize readily and a kidney which has difficulty in excreting calcium.

I am delighted with Dr. Fraser's studies, which confirm and extend some we did about a year ago. We did not have access to human rachitic cartilage and so were hesitant to interpret our observation that rib cartilage from a hypophosphatic patient could not be calcified in vitro.

Perhaps I might venture a comment on the various names which have been offered for this syndrome. Since alkaline phosphatase ordinarily is low in tissue other than bone, perhaps it would be best for the present to regard the condition as a deficiency of enzyme activity, probably genetically determined, with its most obvious manifestation being inadequate mineralization of the abundant but possibly abnormal matrix. This tends to place the skeletal disorder as a metabolic bone disease related to rickets (which is known to be induced by a variety of mechanisms, such as vitamin D deficiency, intestinal insufficiency, and renal tubular insufficiency, all expressing themselves in an abnormality of calcium and phosphorus metabolism) in contrast to quantitatively deficient matrix (as in scurvy and senile osteoporosis) or an excess rate of bone destruction (as in hyperparathyroidism and renal rickets).

DR. ROBERT ULSTROM, Los Angeles: We have studied a case of this type in which the parents are second cousins. I think this adds a great deal of fuel to the fire of its being a genetically determined disease.

DR. J. C. RATHBUN, London, Ont., Canada: I was interested in following the splendid work-up which has gone on in this type of case which we saw in Toronto eight years ago. Unfortunately, in London, we do not have the same case material.

DR. D. FRASER, Toronto, Canada: Dr. Schlesinger has brought up some very useful points. First of all, the case he demonstrated in utero interests me very much. It has been my concept, at least so far as our patient is concerned, that the onset of the disturbance occurred at the time of birth, probably as the result of the withdrawal of some maternal factor, the nature of which I have been unable to define in any way. Certainly, my concept does not fit the findings in Dr. Schlesinger's case.

Dr. Schlesinger also pointed out very well the possible long-term outlook of this condition and has demonstrated improvement in the lesions as the child grows older. At the same time, I agree with Dr. Holt that there are differing degrees of severity, and I suppose there may even be different forms of the disease. Certainly our infant, who is much more severely affected than Dr. Schlesinger's, has shown no signs of improvement after seven months without any demonstrable growth.

Dr. Chown's case, which was reported many years ago, is very interesting. He remarks on the occurrence of convulsions, and as a matter of fact, convulsions occurred also in Dr. Rathbun's case. Indeed this may be part of the disease; I do not know.

I think I cannot comment on Dr. Sobel's review of the genetics, except to thank her for her very excellent survey and to say that if there are any other known cases, I am sure that Dr. Sobel and the rest of us would be interested to hear about them and to know about any genetic relationships. In this regard Dr. Ulstrom's remarks were very interesting and significant.

I should like to comment in closing that today's remarks by Dr. Rathbun, who reported the first case of hypophosphatasia, are of far more than historical interest. His case was very beautifully worked out, and I do not think that much has really been added to his original findings.

The Treatment of Thyrotoxicosis in Childhood with Thiouracil Drugs: Follow-Up on Sixteen Cases. DR. JUDSON J. VAN WYK, DR. MELVIN M. GRUMBACH, DR. THOMAS H. SHEPARD II, and DR. LAWSON WILKINS, Baltimore.

Since the introduction of the antithyroid drugs, all children with diffuse toxic goiter at the Harriet Lane Home have been treated medically. Thiouracil or N-propylthiouracil has been given to 16 patients between the ages of 4 and 13 years. Subsequent subtotal thyroidectomy was performed on four patients. Treatment has generally been continued from two to three years, but has ranged from one to seven years. After discontinuance of treatment six patients have now remained in complete remission for 2½ to 6½ years and two others for 4 and 18 months, respectively. No relapses have occurred with the advent of puberty. In patients who have remained well without therapy, the thyroid gland had decreased to nearly normal size before therapy was discontinued.

Four patients who are still receiving antithyroid drugs are being maintained in a euthyroid state. In two of these patients the thyroid gland remained enlarged or became progressively larger. Dramatic reduction in the size of these glands followed when dessicated thyroid in amounts up to 3 grains (180 mg.) daily was given concurrently with large doses of N-propylthiouracil. These patients are now being maintained in an asymptomatic state, but the ultimate outcome is not known.

Four patients treated medically were subsequently thyroidectomized, one because she developed toxic cutaneous manifestations after four months, and another because of persistent thyroid enlargement and the development of leucopenia after three and one-half years of treatment. The other two patients escaped our supervision and had persistent thyrotoxicosis. One of these children left the country and died postoperatively. All three of the surviving patients developed postoperative hypothyroidism and one hypoparathyroidism.

The results are comparable to those of larger series in adults and those reported by Allen and co-workers in children. The comparative merits of medical and surgical management of thyrotoxicosis during childhood will be discussed.

DISCUSSION

DR. DONALD PICKERING, San Francisco: I should like to call attention to a report by Dr. William Riley, in 1940, which concerned the follow-up to the limit of about 15 years in some 52 female children and some 8 male children, all of whom had the onset of their disease before puberty and half of which had been treated with diuretic drugs and half surgery, the experience surgically first.

There were no mortalities; there were two complicating thyroid states, no evidence in any case of hypoparathyroidism following surgery.

As to the recurrence rate which precipitated the necessity for repeat surgery, I think there were two or three cases in which actually surgery had followed a recurrence during therapy with thiouracil.

In contrast, the interesting point which I think Dr. Riley's publication brought out was that recurrence following a successful initial remission with propylthiouracil can occur as late as 15 or even more years of seemingly normal status, such that it is certainly wise for us to follow these patients for a great deal of time.

I think it is complicated particularly in our environment, where distances are rather great between the patients and the medical center, to effect a reasonably good long-term follow-up. These cases actually were screened out of many more such which we have that element to enter into in our selection of the surgical versus the medical in each case.

I think this is a good exposé of proper medical management in thyrotoxicosis, and I think it was a very enjoyable presentation which Dr. Van Wyk brought out.

I should only caution that surgery in proper hands is still a very valuable tool which we must depend upon not infrequently.

DR. NATHAN B. TALBOT, Boston: I should like to add a few remarks which correspond quite closely to those just presented.

Since 1942, when Dr. Oliver Cope and his associates at the Massachusetts General Hospital commenced the practice of removing all but approximately 1 gm. of thyroid tissue in patients with thyrotoxicosis, we have had quite satisfactory results. There have been no deaths and no serious postoperative difficulties. We are at the moment reviewing the necessity of continuing thyroid substitution therapy in these children. In rough terms it would appear that less than half the group need substitution therapy beyond the postoperative period during which they are routinely given standard maintenance doses for a period of a year or so.

One of the factors which has been of interest to us in trying to choose wisely between prolonged chemotherapy and surgical subtotal thyroidectomy is the matter of providing children with Graves' disease with as nearly a normal childhood and adolescence as possible. In our experience, surgery followed, when necessary, by thyroid substitution therapy has required considerably less medical attention than has the control of active thyrotoxicosis by prolonged treatment with propylthiouracil type drugs.

DR. JUDSON J. VAN WYK, Baltimore: I wish to thank Dr. Pickering for his remarks.

It was 15 years ago, before this Society, that Dr. Reilly reported his follow-up on cases managed surgically and medically during the preceding 25 years. This was before the days of the antithyroid drugs, and it gives us an insight into the natural course of this disease. The most significant statement in his paper, it seems to me, is that "a child never has a total remission." In his cases treated with iodine and bed rest the disease "waxed and waned" in severity over a period of years before it eventually burned itself out. It brings up the question whether we are actually influencing the course of the disease with the newer antithyroid drugs or whether we are only keeping the children in euthyroid status until the disease naturally burns out. This question has not been satisfactorily answered.

As far as his surgical results are concerned, he had an excellent series. Of his 33 patients, 3 had recurrences, 3 had permanent hypothyroidism, 4 had temporary hypothyroidism, and 2 had permanent hypoparathyroidism. It is certainly not my intention to condemn surgery. Also, it is not my intention to admit that the surgeons in Baltimore are incapable of doing a good thyroidectomy. The death in our series occurrred elsewhere, and the remaining three constitute too small a series upon which to evaluate surgical results. They do illustrate that the trend has been toward more radical surgery in this disease.

The matter of distance which he brings up is a local problem, and a very real one in a patient who lives at a distance and cannot be followed closely. I think that, as I stated before, surgery is probably the preferable method of treatment in these cases.

I am glad to hear about Dr. Talbot's cases. I believe you said that about half of your patients are now receiving thyroid substitution therapy, and, of course, this requires medical care and observation for the duration.

The question of a "normal adolescence" which you are talking about is exactly our point in favor of medical management. Whether one is managing hypothyroidism following surgery with regular daily tablets or is regulating hyperthyroidism with tablets three times a day is immaterial. The point is that the hyperthyroid children managed medically achieved an excellent remission which after several years will require no further therapy.

Mechanism of Action of Cortisone and X-Radiation upon Deoxyribonucleic Acid Metabolism and Cell Division. Dr. Charles Upton Lowe and Dr. Royden N. Rand, Buffalo.

The mechanisms whereby x-radiation or cortisone interfere with cell division are obscure. A study of the effect of these agents upon deoxyribonucleic acid (DNA) synthesis seemed a logical way to investigate these mechanisms, since DNA synthesis must precede cell reproduction.

Livers from control and treated rats were analyzed chemically for carbohydrate and DNA content. Enumeration of nuclei per gram of liver was performed, allowing expression of results as changes per cell. The duration of cortisone administration varied from one to five days, while x-radiation consisted of a single L. $D_{.100}$.

The results were interesting and unexpected. Cortisone administration for five days normally causes increase of liver glycogen to a value 10 times that found in controls. However, when animals were first irradiated, the usual accumulation of glycogen was prevented. Both agents altered the DNA content of liver cells. There was an accumulation of DNA five days after x-radiation, while in those animals receiving cortisone alone a significant drop in DNA/cell occurred at the end of five days. It was striking that the increase in DNA/cell, resulting from x-radiation, was prevented by administration of cortisone.

The changes in DNA content could be explained by increased formation or decreased destruction in the case of x-radiation and by increased destruction or decreased formation in the case of cortisone. Experiments were designed to examine which hypothesis was correct. Radiophosphorus (P_{32}) was administered to normal and cortisone-treated rats, to animals subjected to partial hepatectomy after cortisone administration, and to normal animals receiving L. $D_{.100}$ x-radiation. DNA was isolated from liver and the rate of incorporation of P_{32} determined. Both agents were found to decrease the rate of DNA synthesis. The fact that administration of cortisone by itself decreased the rate of DNA synthesis and when given to animals receiving x-radiation prevented an accumulation of DNA suggested that cortisone not only may have caused increased deoxyribonuclease activity, but also interfered with DNA synthesis.

Conclusions.—1. Cortisone and x-radiation interfere with DNA synthesis and alter cell DNA content. 2. Both agents interfere with cell division but via different mechanisms, since, in the first instance, DNA content of the nucleus decreases, while in the second it increases. 3. Interference by cortisone may be due, in part, to increased deoxyribonuclease activity, since in x-radiated animals cortisone prevents accumulation of DNA. 4. Interference by x-radiation may be, in part, the result of altered energy production as glycogen metabolism appears to be defective. 5. The use of both agents in conjunction for therapy of neoplasia is suggested, since they inhibit cell division by apparently different mechanisms.

Dr. Robert A. Aldrich, Portland, Ore.: I should like to ask Dr. Lowe if he would care to do a little speculation.

Have you tried implanting neoplasms into rats and trying out the effect of cortisone and x-radiation to see if there is a differential effect on the DNA in the neoplasms as compared to the normal tissues?

DR. WOLF W. ZUELZER, Detroit: I should like to congratulate Dr. Lowe for his beautiful work. I feel very bold in standing up here at all. The remarks I want to make merely refer to the fact that some observations we have made with cortisone in leukemia fit in awfully well without trying to test whether there is any direct relationship.

But we have used cortisone for a number of years in a manner rather comparable to Dr. Lowe's method of treating rats, and what we do observe with something approaching 100% effect is a hypoplasia of the original leukemic hyperplastic marrow in a matter of one to two weeks; then—and this may have a bearing on Dr. Aldrich's question—the normal erythroid cells and precursors return to a marrow which apparently has undergone a very great diminution, at least in total cell content. Whether the DNA per cell is little affected, or whether this is a quantitative effect on cell reproduction as such is something which, of course, I am in no position to guess at.

But it is interesting that we then have a differential return in which the erythroid precursors begin on high dosage, by which I mean something over 300 to 400 mg. in a 4-year-old child. Then the granulocytes recur, and, whether we continue cortisone in the same dosage or not, the genetic effect Dr. Lowe talks about returns and the original leukemic type of stem cell comes back sooner or later.

But I think this type of observation which Dr. Lowe presented may help us in the effect we observe in this type of malignancy.

DR. RICHARD SMITH, Minneapolis: Dr. Lowe's work continues to demonstrate clearly the value of attempts to interpret physiological phenomena in terms of molecular events. It was extremely interesting.

I have one question. The dosage of cortisone employed by the essayist is very large in relation to the body weight of the rats and to doses which are commonly employed in other experimental animals. I wonder if similar trends toward a decrease in DNA per nucleus could be shown, using smaller doses of cortisone.

DR. CHARLES UPTON LOWE, Buffalo: The comments of the discussers were all interesting, and some of them obviously provocative. I should like to take Dr. Smith's question first.

As far as dose goes, we have not bothered to titrate backward to establish the minimal dose which will produce the changes we are studying. On the other hand, it is quite clear that the animal does not absorb the 25 mg. given each day. I should guess that perhaps 1 or 2 mg. is absorbed. But the tedium required to go backward and find the minimal dose which would produce these effects does not seem worth the trouble at the moment; so, in a sense, this is an apology, not an answer to the question.

Dr. Zuelzer really did not raise any questions, but he does give me an opportunity to add one other point which may be germane to his own observations. You remember, on the slide which showed the effect of x-radiations upon the DNA per nucleus, after the third day there is an abrupt rise in the average DNA and it actually returns to normal and, as I said, in some animals, there is an overshoot beyond the normal. It has been established by numerous people that, when DNA is being actively synthesized, it incorporates radioactive precursors such as phosphorus for the DNA molecule. We have studied this phenomenon during the period of what, on the chart, appears to be active DNA synthesis, and, to our chagrin, we observe no incorporaton of P^{32} on Days 3, 4, or 5; this obviously suggests that either phosphorus-containing precursors were available for the synthesis of DNA, or some new metabolic pathway which is not known had been used following the stimulation of x-radiation. The same thing appears to happen in the cortisone-treated animal.

Dr. Aldrich's question is obviously the most stimulating of all—what would happen to a neoplasm treated in the way we treat normal rats?

We have not attempted the experiment which he suggests, but, quite obviously, we have thought of it. If one may speculate in discussion, I should suspect that the effect of combined therapy would be greater than the effect of one agent alone.

One might even observe that sarcomas which are normally resistant to cortisone might become sensitive to its effect when its administration is combined with tumor-lethal doses of x-radiation.

The Synthesis of Serum Proteins by Human Placenta. Dr. Joseph Dancis, Nancy Braverman, and Bernard Katchen, New York.

Placental slices were incubated with radioactive aminoacetic acid. At the end of incubation, "carrier" precipitates were formed in the incubating medium by the addition of human gamma globulin and serum albumin with the appropriate rabbit antibody. It was considered that if gamma globulin or albumin had been synthesized in the presence of radioactive aminoacetic acid, radioactivity would be incorporated into the protein and found in the corresponding precipitate. Suitable controls were used to exclude nonspecific adsorption. By this method, evidence has been found for the production of gamma globulin but not of albumin.

Human placenta was perfused for eight hours with radioactive lysine. The proteins of the perfusate were then separated by electrophoresis and examined for radioactivity. This gave supportive evidence that gamma globulin and probably certain other globulins are synthesized by placenta, but albumin is not.

Conclusions.—The human placenta synthesizes gamma globulin and probably certain other globulins, but not albumin.

Dr. Robert Good, Minneapolis: I think this is an extremely interesting and provocative study. There are several points, I think, which bear consideration.

First, I presume the incubations were carried on at 37 C, which, of course, is a good temperature for bacterial growth. Particularly if Gram-negative micro-organisms were growing here, aminoacetic acid might be incorporated in the proliferating micro-organisms which could in turn be precipitated by antibody contained in normal human gamma globulin. Since this is a possible source of error, I think it would be interesting to hear what precautions Dr. Dancis has taken to avoid this pitfall. For some time we have been extremely interested in the problem of antibody and gamma globulin synthesis during gestation. Recently we have had an opportunity to approach this problem in a different way. Since our approach is indirect, the results must be considered to be suggestive only.

We have studied a patient with acquired agammaglobulinemia who became pregnant. We had a chance to stimulate her with antigen prior to her pregnancy, again during the first trimester of her pregnancy, and once again during the third trimester. To the first two stimulations, she formed no demonstrable antibodies; during the third, she formed a small amount of antibody, but did not increase her gamma globulin concentration significantly. The problem was from whence came the antibody in this patient with agammaglobulinemia and immunologic paralysis. We were surprised to find, when the fetus was delivered, that the baby had electrophoretically defined agammaglobulinemia and contained less antibody than the mother. This observation indicated that the fetus was not producing either agammaglobulin or antibody.

The mother's titer dropped off rapidly after she delivered the placenta and the baby. It thus appeared that the antibody formation was a vault of the activities of the gestational product or event. We approached the problem of where the antibody was produced in a morphological fashion.

We studied the maternal lymph nodes and bone marrow in response to antigenic stimulation prior to pregnancy, during first trimester, during third trimester, in the neonatal period, and four months after delivery. In no instance were plasma cells to be found. The stimulus used regularly produced plasmacytosis in both bone marrow and lymph nodes of normal persons. We studied the bone marrow and inguinal lymph nodes of the baby in the immediate neonatal period. Plasma cells could not be found. We provided the baby with antigenic stimulation in the neonatal period, and neither plasma cells nor antibody were produced. Surprising to us was the finding that the placenta contained plasma cells, the morphological sign of antibody, and gamma globulin synthesis.

So we too think the placenta may be able, under certain circumstances, to form antibodies and gamma globulin. I think these studies Dr. Dancis has done represent a big step forward, and he is to be congratulated for his careful observations.

Dr. Joseph Dancis, New York: I have been asked by the chairman to be brief: I have known of Dr. Good's case for a few months now and am delighted that he has presented it. I believe that our data, collected under the artificial conditions of an in vitro experiment, are supported by his data.

In reference to his question concerning bacterial contamination, we have not searched for the presence of bacteria in the medium. However, we have added antibiotics to discourage such

growth, and the immunological approach that was used to demonstrate the specificity of the protein synthesized, namely, human gamma globulin, should also exclude bacterial proteins.

The Hypothyroid Infant and Child: Aspects of Clinical Management. Dr. Donald E. Pickering, Dr. Lee B. Lusted, and Dr. Delbert A. Fisher, San Francisco.

The clinical management of hypothyroidism in infancy and childhood is reviewed with reference to the care and study of approximately 30 such children over the past four years in the University of California Pediatric Endocrine and Metabolic Clinic. Data to be presented from these cases, as well as from parallel studies conducted in this laboratory on athyroid infant rhesus monkeys, emphasize those aspects of thyroid physiology which allow a more rational basis for therapy.

The clinical stigmata of delayed or inadequate therapy and the most practical clinical and laboratory criteria, serially determined, by which confirmation can be made of the diagnosis and the adequacy or inadequacy of therapy are presented. The particular efficacy of sodium *l*-thyroxine as a therapeutic agent in the pediatric age group is demonstrated.

In the patients presented, as in the athyroid infant monkey, it has been observed that major metabolic and clinical signs of thyroid deficiency may be controlled with doses of hormone significantly smaller than those required to promote optimal central-nervous-system and skeletal growth and maturation. The important discrepancy in tissue response may be largely responsible for the present pessimism and uncertainty in evaluation of long-term appraisal of replacement therapy in congenital athyroidism.

It seems of primary importance that initial therapy in the congenital athyrotic infant must be directed toward supplying sufficient thyroxine for early, critical central-nervous-system and skeletal growth and development.

The Changing Pattern of Adrenal Corticosteroids from Birth to Maturity. Dr. Mary Thornton, Edwin R. Hughes, M.S., Dr. Robert S. Ely, and Dr. Vincent C. Kelley, Salt Lake City.

It is generally accepted that in human subjects susceptibility to disease and physiologic responses to "stress" depend to a considerable extent on the age of the individual. In addition, in certain human diseases (i. e., rheumatic fever, nephrosis, etc.) the characteristic clinical symptomatology varies with the patient's age. Similarly, it has been commonly observed that the response of experimental animals to a variety of stimuli is influenced by differences in age as well as in species. The factors involved in these age differences are poorly understood. Adrenal cortex hormones are known to influence the response to "stress." It seems possible that if there were any difference in the hormones elaborated by the adrenal cortex at different ages this might be one factor contributing to the age variability in response.

In the present investigation the adrenal cortex hormone pattern has been studied in various species from birth to maturity. Determinations were done by the fluorometric technique of Sweat. By this method the concentrations of the two principal adrenal cortex hormones, 17-hydroxycorticosterone (Compound F) and corticosterone (Compound B), are measured independently. Four species—rat, guinea pig, rabbit, and man—were studied. In agreement with previous studies, definite species differences were observed. In addition, within each species the total concentrations of the hormone measured as Compound B and Compound F varied with age following a definite pattern. This age pattern was different in different species.

In the technique employed, the steroids are separated by column chromatography. The concentration of steroids in each fraction then is quantitated fluorometrically. In control studies, the levels of steroids measured by this technique are comparable to those obtained by other methods. However, there is reason to believe that under certain circumstances other steroids, less well-characterized than Compounds B and F, may be present in appreciable quantities and may influence the apparent concentrations of the latter compounds. Because the possibility exists that such steroids are present here, an attempt now is being made to characterize more definitely the steroids measured as Compound B and Compound F in the various experimental groups. Despite the possible influence of these other steroids on the measurement of Compounds B and F, the data clearly demonstrate that the steroid pattern in each species changes with age.

Among the implications of these findings are the following: 1. It is advisable in designing animal experiments concerned with adrenal function to control the factor of age. 2. Many discrepancies among data obtained in studies related to adrenal function may reflect species or age differences in the experimental animals employed by the investigators. 3. Differences in the characteristic clinical patterns of disease and in responses to "stress" at different ages may reflect, to some extent, the changing pattern of adrenal corticosteroids.

Reversible Respiratory Depression in Salicylate Intoxication. Dr. Robert W. Winters, Dr. James S. White, and Dr. Nelson K. Ordway, Chapel Hill, N. C.

Although hyperpnea is a familiar feature of salicylate intoxication, the occurrence of severe respiratory depression has not been generally recognized, possibly because it has been almost invariably associated with a fatal outcome. This paper reports a study of the successive acid-base disturbances encountered in a young infant with salicylism complicated by respiratory depression who was successfully treated.

The patient was a 3-month-old white girl who received an overdosage of acetylsalicylic acid for a minor respiratory infection. On admission to the hospital, the child was critically ill, excited, and hyperpneic; the initial chemical determinations in the blood revealed a carbon dioxide content of 8.3 mM/liter and a pH of 7.03, indicating a state of metabolic acidosis with but partial respiratory compensation. Pulmonary edema occurred shortly after admission but was controlled by aminophylline. Following this, the respiratory rate progressively fell to virtual apnea. Stupor followed by coma accompanied by cyanosis replaced the initial excitement. Chemical studies now revealed a carbon dioxide content of 17.9 mM/liter and a pH of 6.80. The child received a rapid infusion of sodium bicarbonate and in addition was given oxygen and artificial ventilation in an infant rocking bed for 28 hours. Following these measures, she regained consciousness, her color improved, and eventually she resumed normal breathing without assistance. Serial determinations of pH and carbon dioxide content revealed a progressive return to normal values. She apparently recovered completely, and there has subsequently been no indication of residual central nervous system damage.

The chemical findings on this patient provide evidence for a rational explanation of the metabolic acidosis in salicylism and a possible mechanism of the respiratory depression. The data demonstrate that the metabolic acidosis arose in this patient from an accumulation of fixed anions in the form of chloride, phosphate, salicylate, and undetermined acids. The effect of this accumulation was the displacement of bicarbonate to such a level that in spite of the lowered carbon dioxide tension, acidosis supervened. The respiratory depression is interpreted to be a manifestation of a more general effect upon the central nervous system of intoxication by salicylate. This may have been potentiated by the concurrence of elevated carbon dioxide tension, severe acidosis, and anoxia.

PAPERS READ BY TITLE

Origin of Species in Micro-Organisms: Use of Transformation as a Tool. Dr. Hattie E. Alexander and Grace Leidy, A.B., New York.

Change in heritable traits of micro-organisms by interaction of deoxyribonucleic acids (DNA's) of two genetically different cells has been held to be limited to organisms within the same species. This view is prevalent among those who have used transformation in bacteria as well as those who have used recombination in bacterial viruses for inducing a heritable change.

It has been demonstrated in our laboratory that DNA controlling streptomycin resistance in one specific type of Hemophilus influenzae can induce resistance in a heterologous type. However, the homologous streptomycin resistance DNA induces streptomycin resistance in a higher proportion of a sensitive homologous type of H. influenzae than in a sensitive heterologous type of H. influenzae. The DNA's or hereditary determinants controlling streptomycin sensitivity or resistance would seem to be more complementary if they are derived from the same population.

These results stimulated interest in the use of the streptomycin resistance DNA as a tool for exploring the relationship among different species of Hemophilus as well as among different families of bacteria. The results can be expected to yield information on origin of different species.

Three different species of Hemophilus have been used for this purpose: H. influenzae, H. parainfluenzae, and H. suis. Bacteriologists have separated the first two on the basis of certain growth requirements; they play very different roles as human pathogens. The third species, H. suis, is differentiated in a definitive way only by the sources from which it is cultured. It is a swine pathogen. The latter organism is of interest because it has been alleged that the swine pandemic which occurred for the first time in this country in 1918 was the origin of the human pandemic and because both H. suis and the swine virus are required to produce the disease in swine.

DNA containing extracts were prepared from streptomycin-resistant cells of each of the six types of H. influenzae, from a nontypable H. influenzae isolated from the normal nasopharynx, from H. parainfluenzae, and from H. suis. The cultures of cells resistant to 1000γ of streptomycin per milliliter, from which the DNA's were derived, were obtained by selecting in the presence of stretopmycin a one-step, spontaneously occurring resistant mutant from a large sensitive population. Each of these varieties of organisms was also used as recipient cells; suitable populations were exposed to the DNA isolated from highly resistant cells of each of these organisms, and the proportion of cells in which streptomycin resistance was induced was measured.

The results suggest that the DNA's of a homologous type are most complementary. The proportion of cells in a nontypable H. influenzae which are susceptible to induction of streptomycin resistance suggests the specific type from which it has been derived. A transfer of streptomycin resistance from resistant H. influenzae to sensitive H. parainfluenza and H. suis and from resistant H. parainfluenzae and H. suis to sensitive H. influenzae has been regularly demonstrated, but the proportion of cells susceptible to this change is very low. It has not been possible to demonstrate exchange of heredity determinants between H. parainfluenzae and H. suis. Among the species now classified as Hemophilus, the degree of incompatability between the DNA's of some groups raises the question whether they belong in the same family. Whether H. influenzae is a cousin or grandchild of H. suis or H. parainfluenzae is under study.

Defect of Antihemophilic Globulin in von Willebrand's Disease. J. M. M. DARTE, Toronto, Canada.

Von Willebrand's disease is a hereditary hemorrhagic diathesis characterized by a prolonged bleeding time and abnormal capillary function. The platelets are morphologically and numerically normal. In those instances where tests of platelet function have been studied, these are normal. Clotting and prothrombin times and prothrombin consumption indices have been reported as within normal limits by most workers. Other than abnormal capillary function no report of specific defect of coagulation factors has been detected. This is a report of a deficiency of antihemophilic globulin occurring in an individual who otherwise presented the classical picture of von Willebrand's disease. A similar but less marked deficiency was demonstrated in the mother. A sister had died 14 years previously from severe epistaxis.

The patient was a 9-year-old boy who had bruised and bled easily for seven years. For two months he had suffered from recurrent spontaneous pharyngeal hemorrhages at night. Physical examination revealed no abnormality. The bleeding time was prolonged for 15 minutes or longer on repeated examinations. The capillary resistance test was positive. Clotting time, prothrombin time, clot retraction, and platelet counts were all normal. The prothrombin consumption index was at the upper limit of normal. The thromboplastin generation test on two occasions revealed a moderate deficit of antihemophilic globulin. His plasma failed to correct the recalcification time of the plasma of two patients with hemophilia as well as did normal plasma.

The patient's mother gave no history of hemorrhagic tendency. However, the bleeding time was prolonged to 15 minutes, and the capillary resistance test was positive. The thromboplastin generation curve showed a mild defect in antihemophilic globulin. The patient's sister had died in 1942, at the age of 5 years, but previous to her death she had been examined at the Hospital for Sick Children at age 3½ because of recurrent severe nose bleeds. At that time the capillary resistance test was positive, the bleeding time markedly prolonged, and platelets were normal on smear.

These three cases give a classical picture of von Willebrand's disease, except for the demonstration in the mother and son of a deficit in antihemophilic globulin. Until now a

deficit in antihemophilic globulin has only been described in true hemophilia. These findings suggest that there is a variant of von Willebrand's disease which is associated with deficiency of antihemophilic globulin. This deficiency in antihemophilic globulin does not appear to be inherited as a sex-linked recessive, as is the inheritance of true hemophilia.

Epidemic Diarrhea Among Infants Associated with the Isolation of a New Serotype of Escherichia Coli: E. Coli 0127: B_8. Dr. Merlin L. Cooper, Edward W. Walters, M.S., Helen M. Keller, M.S., Dr. James M. Sutherland, and Dr. Hollis J. Wiseman, Cincinnati.

A type of Escherichia coli previously unidentified was isolated from 44 of 145 infants during an outbreak of epidemic diarrhea and from one nurse among 82 adult personnel. This E. coli was forwarded to Dr. W. H. Ewing for antigenic study, and it was his conclusion that our E. coli was a particular serotype with a new "O" antigenic group which most likely would be designated by Dr. F. Kauffmann in Denmark as 0127. Dr. Kauffmann confirmed the opinion of Dr. Ewing, and this serotype is now designated E. coli 0127 : B_8.

Severe epidemic diarrhea associated with the presence of E. coli 0127 : B_8 was characterized by the sudden development of extreme abdominal distention among some of the infants; explosive onset of diarrhea, and the presence of a pungent, musty, objectionable odor not noticed around other diarrhea patients.

Neomycin was used orally for the specific treatment of patients with diarrhea. The average dose was 40 mg/kg/day for the positive patients and 46 mg/kg/day for the negative patients.

Twelve of twenty-two positive patients treated with neomycin alone or in addition to other antibiotics continued to show the presence of E. coli 0127 : B_8 after discontinuing neomycin; however, only two of these patients had a recurrence of diarrhea, both having had negative cultures while receiving neomycin.

The administration of neomycin prophylactically to every infant on the two wards, regardless of their clinical condition, was followed by a decreasing incidence of diarrhea and decreasing detection of E coli 0127 : B_8. The dose of neomycin was 40 to 50 mg. per kilogram per day. It is our feeling that neomycin administered orally was of definite clinical value therapeutically and prophylactically but in the dosage used was inadequate bacteriologically.

Four deaths occurred among the 44 infants whose rectal swab cultures were positive for E. coli 0127 : B_8, and necropsy studies were made on each. A hemorrhagic enteritis was present terminally in three infants, and the cause of death in the fourth infant was a congenital heart condition. Death of one negative patient may very likely be attributed to a severe diarrhea.

All sera from patients and personnel failed to show the presence of any agglutinins for E. coli 0127 : B_8.

In vitro sensitivity tests showed that the order of decreasing bactericidal effectiveness of five antibiotics for E. coli 0127 : B_8 was polymyxin, neomycin, chloramphenicol, tetracycline (Achromycin), and oxytetracycline (Terramycin). All strains were resistant to dihydrostreptomycin and sulfadiazine sodium. Only the last strains isolated from two patients showed increased resistance to neomycin, fourfold and sixteenfold, when compared with the first strains isolated from the same patients.

Conclusions.—A bacteriological and clinical study of an epidemic of infantile diarrhea revealed a new serotype of E. coli, E. coli 0127 : B_8, present in rectal swab cultures of 44 infant patients and one nurse. Neomycin administered orally was of clinical value therapeutically and prophylactically but was inadequate bacteriologically in the dosage used, since rectal swab cultures from 12 of 22 infants continued to show the presence of E. coli 0127 : B_8 after discontinuing this antibiotic.

Experience with Needle Biopsy of the Liver in Infants and Children. Dr. Ogden C. Bruton, Seattle, Wash.

Needle biopsy of the liver in adults has been established as a useful adjunct in diagnosis. In infants and children this procedure has been ignored by most, condemned by many, and used by few of us. Fifty patients varying in age from 19 days to 10 years were selected as suitable for needle biopsy of the liver. Histological study of the biopsied tissue helped (1) to establish the status of the liver prior to surgery in Banti's syndrome, (2) to establish the diagnosis in some patients with enlargement of the liver due to unknown cause, (3) to aid in the differential diagnosis of jaundice occurring in the neonatal period, (4) to establish the extent of liver involvement in certain systemic diseases, and (5) to determine periodically the status of the liver for

prognostic purposes. Examples of each of these categories will be given. Contraindications and techniques will be discussed and the ease with which the procedure may be done without general anesthetic on the infant prior to the "fear reaction" age will be pointed out. The data presented indicate that needle biopsy of the liver is a useful adjunct for diagnosis and study in infants and children, and when used with discretion is safe enough to merit favorable consideration.

Size of the Acetabular Angles at Birth, at Six Months, and at Twelve Months: Significance in the Identification of Congenital Dysplasia of the Hip; A Preliminary Report. Dr. John Caffey, Dr. Rose Ames, Dr. William A. Silverman, Dr. Charles T. Ryder, and Dr. Garry Hough, New York.

Prophylaxis of congenital dislocation of the hip is widely practiced in the United States, and it is based on the hypothesis that there is an early predislocation phase, congenital dysplasia, which can be identified during the first weeks of life, prior to actual dislocation. Limitation of abduction on the affected side with extra folds of skin in the thigh are the principal clinical signs of congenital dysplasia. Enlargement of the ipsilateral acetabular angle, determined by the method of Helgenreiner, is the cardinal radiological sign and has come to be the most important single finding. Standards for the upper limit of normal have not been satisfactorily established; 32 degrees, 30 degrees, and even 25 degrees have been used as the upper limits of the normal range.

We are now engaged in a longitudinal radiographic and clinical study of the hips of more than 1000 infants for the purpose of establishing the mean size of the acetabular angles and the range of normal variation at birth, 6 months, and 12 months of age.

Currently we have completed observations on 1180 newly born infants, 800 six months of age, and 600 twelve months of age. Analysis of these data indicates that the mean size of the angles at birth approximates 28 degrees. Extremes encountered this far are 44 degrees and 8 degrees. In 180 hips in which the neonatal angles were 36 degrees or more (36 to 44), the angles in all had diminished at 6 months of age without dislocation. In two cases in which the angles were 34 degrees at birth, dislocation had developed by the sixth month of life. In neither of these were there clinical signs of predislocation during the neonatal period or at 6 months of age, when dislocation was clearly evident radiographically.

In the Negro infants, who formed a substantial segment of the entire group, the acetabular angles were just as large as in white infants, notwithstanding the fact that dislocation of the hip is all but unknown in Negroes.

Clinical examination disclosed extra folds in the thighs in 21% of newly born infants, not one of whom developed later dislocation. There was no correlation between the size of the acetabular angles and the presence of extra folds in the skin. In 70 infants, abduction at the hip was decreased 15 degrees or more on one side. There was no correlation between the size of the acetabular angles and limitation of abduction.

Our data indicate that the normal acetabular angles are considerably larger than the standards for normal in current use, and that congenital dysplasia of the hip is being diagnosed far too frequently. For the same reason prophylactic treatments for congenital dislocation of the hip are being given to large numbers of healthy infants.

Our data suggest that congenital dysplasia of the hip cannot be identified by the size of the acetabular angles and that the predislocation phase of congenital dislocation of the hip, based on enlargement of the acetabular angles, is a myth.

We have found the acetabular angles to be exceptionally small, the ilial wings to be exceptionally large, and the ischial rami exceptionally long in several neonatal and early infantile Mongoloids. These promise to be consistent stigmas of Mongolism at an age when diagnosis is most difficult.

In several normal infants, we have found irregular mineralization of the superior pubic rami from two or more ossification centers, a hitherto unrecognized normal variant of the normal neonatal pelvis.

Vitamin A Deficiency in Infants. Dr. Murray H. Bass and Dr. Joseph Caplan, New York.

Vitamin A deficiency is an unusual occurrence in infancy, because the average infant, being fed on milk, obtains enough of this vitamin in its food. However, infants allergic to milk who are put on milk-free diets may develop vitamin A deficiency if no vitamin supplement is given. Such

a case is described in a 7-month-old infant who was unwittingly kept on a diet lacking in vitamin A for five months. Following a mild upper respiratory infection the child developed hematuria for which he was hospitalized. Severe anemia and corneal clouding with ulceration were discovered. A few days later high fever, and neurological signs with a markedly bulging fontanelle appeared. The cerebrospinal fluid was entirely normal and rapidly reaccumulated. Diagnoses of subdural hematoma, multiple cerebral septic emboli, and thrombosis of the saggital sinus were suggested. Subdural tap resulted in negative findings. The infant's general condition rapidly deteriorated. The curious combination of anemia, corneal lesions, hematuria, and hydrocephalus was recognized as a syndrome due to vitamin A deficiency. Large parenteral doses of vitamin A led to prompt complete recovery within a week.

A second case is recorded of an icteric infant with proved absence of the bile ducts who suddenly developed bulging fontanelle with normal spinal fluid. Blood vitamin A level was very low. With large parenteral doses of vitamin A the signs of hydrocephalus disappeared. It is suggested that the sudden appearance of the increased intracranial pressure in this case was due to deficiency of vitamin A.

From these two cases and the few we have been able to find in the literature it is evident that vitamin-A-deficient infants may present the following symptoms:

1. Retardation of mental and physical growth.
2. Anemia with or without hepatosplenomegaly.
3. Tendency to infection.
4. Epithelial metaplasia.
   (*a*) In the eye: xerophthalmia and keratomalacia.
   (*b*) In the urinary tract: pyuria, hematuria, and excessive numbers of epithelial cells in the urine.
   (*c*) In the genital tract: cornified vaginal epithelium.
   (*d*) In the respiratory and digestive tracts.
5. Hydrocephalus with increased cerebrospinal pressure with or without isolated cranial nerve paralyses.
6. Endocrine disturbance: gynecomastia.

These symptoms are discussed in detail.

The sudden appearance of unaccountable signs of increased cerebrospinal fluid with bulging of the anterior fontanelle should suggest some irregularity in vitamin A metabolism, since this may occur both in hypo- and hypervitaminosis A. The increased pressure in these cases is not due to disproportion between the growth of the skull and the brain, as has been found in experimental animals. The suddeness of the appearance of the bulging fontanelle and its equally rapid disappearance with changes in vitamin A administration points rather to some disturbance of secretion or absorption of the cerebrospinal fluid as the underlying etiologic mechanism.

Conclusions.—Vitamin A deficiency in infants may cause bizarre clinical pictures and may lead to very serious disease. It is amenable to very rapid cure. Pediatricians and allergists should be reminded and warned by the cases here described that when allergic infants are placed on milk-free diets, the addition of vitamin A must not be overlooked.

Pseudosenilism of Progeria. Dr. I. Pat Bronstein, Dr. Ira M. Rosenthal, Dr. Samuel Pruzansky, and Dr. Heyworth N. Sanford, Chicago.

Prolonged study of a case of progeria (Hutchinson-Gilford syndrome) raised the question of whether true premature aging is actually present in this disease. The patient was a girl whose growth and development were followed for a period of 10 years until her accidental death at the age of 11 as a result of a head injury. She attained a height age of 3½ years and a weight age of 1½ years.

The feature of patients with progeria most suggestive of senilism is their facial appearance, whih resembles that of an edentulous aged person. Cephalometric studies, not previously reported in this disease, were performed on this patient. Analysis of the roentgenograms revealed that, while neurocranial development was essentially normal, there was gross retardation of the growth of the splanchnocranium. The resulting diminution in the vertical height of the face largely accounts for the senile facial appearance of patients with progeria. The dental development of this

patient was retarded, and there was no eruption of the second deciduous molars. The crowns of the unerupted teeth crowded the mass of the body and ramus of the underdeveloped jaws.

Almost total alopecia was found in this child and contributed to her senile appearance. It should be noted, however, that the alopecia found in progeria affects both sexes equally and is quite different in appearance and origin from the baldness frequently found in old men.

Atherosclerosis is commonly found in progeria. In our patient, serum lipoproteins were determined by the Gofman technique. Standard S_f 0-12 was 492 mg. per 100 cc., and standard S_f 12-400 was 221 mg. per 100 cc. The atherogenic index was 88. These results would indicate a relationship between elevated serum lipoproteins and the development of atherosclerosis in patients with progeria. It is of interest that elevation of serum lipoproteins was found in an individual with a paucity of adipose tissue, since high lipoprotein levels are more often found in obese persons. We believe that a metabolic disturbance accounts for the development of atherosclerosis in progeria and that it is not the simple result of aging.

A radioiodine uptake, not previously reported in cases of progeria, was normal. This suggests a normal secretion of thyrotropic hormone and is further evidence against the theory that pituitary malfunction is the cause of progeria.

Serial psychological studies were made. Intelligence was normal. None of the psychological changes characteristic of senilism were found in this patient.

The autopsy findings are of special interest, since the accidental death of the patient afforded the opportunity to study the pathology before the disease itself caused death. The autopsy revealed that the immediate cause of death was a severe epidural hemorrhage. A severe degree of the atherosclerosis for the child's age was found in the coronary arteries, the aorta, and the mesenteric arteries. The pituitary was considered normal. None of the histological changes characteristic of senilism were found in the skin. Limitation of motion of many of the joints was present during life. Despite this, the synovia of the joints examined at autopsy were normal, and no findings suggestive of senile arthritis were present. The periarticular tissues were unusually fibrous.

Analysis of the above data leads us to believe that true premature aging is not found in progeria, but that the senile appearance of these patients is the result of a peculiar growth disturbance associated with severe nutritional and metabolic dysfunction, the nature of which is unknown.

A Controlled Study of the Influence of Water Mist upon Obstructive Respiratory Signs, Death Rate, and Autopsy Findings Among Premature Infants. DR. WILLIAM A. SILVERMAN and DR. DOROTHY H. ANDERSEN, New York.

The obstructive respiratory disorders of newly born premature infants have been treated by placing these infants in environments that are supersaturated with water. It has been the widespread practice to place all premature infants in mist-filled incubators in an attempt to prevent the respiratory symptoms which they so commonly develop. Despite favorable reports concerning the efficacy of this mode of treatment, there have been no published reports presenting acceptable proof of therapeutic benefit. A controlled clinical trial was planned to attempt to obtain objective evidence of the therapeutic effect of mist upon premature infants.

Two hundred infants admitted to the Babies Hospital over a 10-month period of time were entered into the study. By means of a series of prearranged blind random sequences each infant was alloted to either the treated or control group. The treatment regimen consisted of exposure of the infant to a mist-filled atmosphere of nebulized distilled water from the time of admission until the age of 72 hours. The control regimen consisted of exposing the infant to an atmosphere maintained at standard operating conditions (90% to 100% relative humidity). All other conditions, such as oxygen concentration (30% to 38%) and heat (86 to 88 F), were maintained in a comparable manner in the two groups. The conditions of the trial were terminated at the age of 72 hours. Observations of respiration were made by means of an objective scoring scheme at six-hour intervals. This "retraction score," the respiratory rate, the death rate, and the autopsy findings constituted the objective criteria by means of which the two groups were evaluated.

It was shown that the two groups were reasonably comparable with respect to many characteristics effecting death risk. There was no significant difference between the respiratory signs of the surviving infants in each of the two treament groups. Moreover, there was no significant difference between the death rates in the two groups, and the autopsy findings among those who died were comparable.

Analysis of the Clinical Results from the Surgical Creation of Pulmonary Stenosis in Nineteen Patients with a Large Communication Between the Left and Right Ventricle. Dr. J. Francis Dammann Jr. and Dr. William H. Muller Jr., Charlottesville, Va.

The basic concept involved in the surgical creation of pulmonary stenosis needs reemphasis. In patients with a large communication between the great vessels or ventricles, the right and left ventricles function as one. A common systolic pressure is generated in both ventricles and consequently in both aorta and pulmonary artery. Therefore, the relative volume of blood flow to the lungs and to the body is dependent upon the peripheral vascular resistance. At birth the resistance in the two circulations is essentially the same. Shortly after birth there is a progressive increase in lumen size and decrease in wall thickness of the small pulmonary artery, with a consequent decrease in pulmonary resistance. As resistance falls, pulmonary blood flow increases. High-output cardiac failure may result. In patients who survive cardiac failure, progressive sclerotic changes take place in the pulmonary arteries, with a consequent rise in pulmonary vascular resistance and fall in pulmonary blood flow. These vascular changes may progress to the point where pulmonary resistance is actually higher than systemic resistance. If this occurs, cyanosis becomes prominent.

The surgical creation of pulmonary stenosis was devised to place an artificial resistance in the pulmonary vascular trunk, thereby increasing total pulmonary vascular resistance and decreasing total pulmonary blood flow. The presence of such an artificial resistance, in addition, removes the stimulus to progressive arteriolar thickening and permits the pulmonary bed to evolve in a normal fashion.

Since July, 1951, twenty-two operations for the creation of pulmonary stenosis have been performed on nineteen patients. The type of cardiac malformation present varied. Eight patients had a large ventricular defect with a common systolic pressure in both the right and left ventricles. Four patients had a medium-sized ventricular defect with a significantly lower pressure in the right ventricle. Four patients had anatomical single ventricles. Two patients had an atrioventricularis communis, and one patient—misdiagnosed as a large ventricular defect—was found to have a large auricular defect with a congenitally malformed mitral valve. The common denominator in all was a communication between the right and left ventricles sufficiently large to raise the pulmonary systolic pressure and pulmonary blood flow. The creation of pulmonary stenosis was advised in order to diminish the work of the heart by reducing the pulmonary blood flow or to prevent progressive pulmonary arteriolar changes.

Among the 19 patients, there were 8 fatalities. Of these, three occurred before the chest was opened and two occurred because the pulmonary artery, for technical reasons, could not be narrowed sufficiently. One patient died of paroxysmal dyspnea 5 months postoperatively, one of cerebral thrombosis 3 days postoperatively, and one of aspiration pneumonia 10 days postoperatively. Those patients who have survived have been, without exception, markedly benefited. Cardiac failure has disappeared, exercise tolerance has greatly increased, and growth and development have followed a more normal course.

An analysis of our results strongly suggests that the creation of pulmonary stenosis, when properly used, can be of great benefit.

The Bacteriology of Acute Otitis Media in Infancy. Dr. Edward A. Mortimer Jr. and Dr. Reich L. Watterson, Cleveland.

The purposes of this study were to define better the bacterial agents responsible for otitis media in children under 2 years of age and to correlate throat and nasopharyngeal flora with the organism found in the middle ear.

One hundred four patients thought to have acute purulent otitis media were studied. Nasopharyngeal cultures were obtained by passage of a wire cotton swab through the nose, and pharyngeal cultures were obtained in standard fashion. Rabbit-blood agar was used entirely. Under direct visualization the middle ear was aspirated through the tympanum, using a long No. 20 short bevel needle and oral suction. Any material obtained was examined directly for the presence of purulent exudate and organisms and inoculated into blood agar and into a modified Levinthal's broth. In an effort to differentiate those organisms present in the middle ear from those picked up by external contamination, a cotton toothpick swab was wiped over the drum surface prior to aspiration and inoculated onto blood agar. Cultures were incubated aerobically.

In 100 of the 104 patients the middle ear was aspirated; four drums had acutely perforated. In 36 instances no purulent exudate was obtained and cultures were sterile. The cultural results in the 68 patients from whom middle ear exudate was obtained are tabulated below.

Sterile on culture	25
Pneumococci alone	27
Pneumococci and Hemophilus influenzae	4
Hemophilus influenzae alone	9
Beta hemolytic streptococci	2
Unidentified Gram-negative Coccobacillus	1

Diphtheroids and especially staphylococci were isolated frequently from middle-ear cultures but could not be incriminated as causative agents when correlated with cultures of the external drum surface.

Pneumococci were isolated from the pharynx and/or nasopharynx in 82%, H. influenzae in 85%, and beta hemolytic streptococci in 6% of all patients. Because at least two of these three organisms were obtained from the nasopharyngeal and/or pharyngeal cultures of 70% of all patients, and because of the occasional apparent absence in these sites of the ear organism, it was not possible to identify the infecting agent in the ear by inference from the upper respiratory tract flora with any degree of reliability.

The Pediatrician in a Supportive and Consultative Relationship to General Practitioners in a Rural Medical Center: A Possible Way Favorably to Influence Child Health in Thinly Settled Areas. DR. ANDREW D. HUNT JR., New York.

As emphasized in the Report of the American Academy of Pediatrics in 1949, "Child Health Services and Pediatric Education," 75% of the children in the United States are under the care of general practitioners. The geographical distribution of pediatricians, as indicated in the Academy's survey, is such that a dearth of child specialists exists in rural areas. A basic reason for such a distribution would appear to be the unlikelihood of the success of a traditional pediatric practice in a thinly settled rural area.

Hunterdon County, New Jersey, comprises an area of 400 square miles of farm land, has a population of 42,000, and is located midway between Philadelphia, and New York. Although adjacent to semiurban areas, its medical status prior to 1952 was essentially rural, with no practicing specialists, no hospital, and 25 general practitioners carrying the largest part of the medical load. The presence of but two towns of population larger than 3000 had made the county an undesirable area for the establishment of specialists' practices.

The community with some Foundation support, therefore built the Hunterdon Medical Center, a 120-bed hospital and health center. Eleven full-time specialists were recruited and work essentially as a group practice, with all department chiefs receiving identical salaries.

These specialists operate in a purely consultative and supportive role to the general practitioners, making no house calls and seeing patients only as referrals. The specialists have faculty appointments at a New York medical college, and a house staff is provided by virtue of this relationship.

The basic difference between this set-up and the British system and other rural specialists' groups in the United States is the participation of the general practitioners. The general practitioners are staff members, have representation on the governing Medical Board, and may hospitalize their own patients, under a flexible supervision by the respective specialists.

At the pediatric level, a continuing postgraduate educational program is thus established, high standards of neonatal and inpatient pediatric care are achieved, and the integrity and basic status of the general practitioner as the first echelon of medical care are maintained.

In general, after 18 months of operation, the experiment shows signs of success, with generally good acceptance by the general practitioners and the specialist group being self-supporting.

As anticipated, pediatrics, an area in which the general practitioner feels competent, practiced in this way has posed interesting and, at times, difficult problems.

It is hoped that this organization may serve as prototype for similar centers in other rural or semirural areas. From the pediatric standpoint, it appears to provide a setting in which the pediatrician can maintain his status as a specialist, enjoy university affiliation, and exert his influence more widely in the community than is possible in the traditional practice situation.

Summary.—A rural medical center is described in which a well-balanced specialist group, in a new 120-bed hospital, works in a supportive, educational, and consultative way with the general practitioners who are staff members. This provides a setting in which a pediatrician can operate effectively in an area where traditional practice would be very difficult.

Results and Observation on Fifty Consecutive Cases of Tuberculous Meningitis Treated with Antibiotic Therapy and PPD. Dr. G. H. Nickerson, Montreal, Canada.

In June, 1950, it was evident that the treatment of children with tuberculous meningitis in Montreal was essentially a failure. A review of the repeated failures of therapy made certain principles evident:

1. Regardless of the patient's "good clinical condition," "almost normal," chemistry and cell content of the cerebrospinal fluid were still abnormal.

2. Treatment must be maintained until the C. S. F. becomes normal and longer than the three to four months of therapy heretofore employed.

3. Prevention of formation or removal of the tuberculous exudate obstructing the free flow of C. S. F. at the base of the brain was fundamental to recovery.

4. Tubercle bacilli must be eradicated from the C. S. F. more quickly than previously.

5. More rapid and certain diagnostic bacteriology must be developed both for early bacteriological diagnosis and as an indicator to the efficacy of therapy.

To this end a plan of therapy was devised incorporating streptomycin and PPD, essentially as proposed by Smith and Cairns in 1950. An unprecedented initial recovery rate of 80% was observed, but a number of children revealed complications of therapy and the disease, namely, deafness, atrophy of the optic nerves, orthopedic deformities, and varying degrees of intellectual impairment. This paper presents the experience with 50 consecutive children treated for tuberculous meningitis using antibiotic therapy and PPD. During the past year the rates for mortality and sequelae have been reduced to zero. It is emphasized that antibiotic therapy alone, as it is, will not in itself effect some patients. Several other recognized principles of therapy are presented, and without their recognition recovery may not be anticipated nor sequelae prevented.

Hemolysis in Hydrogen Peroxide of Red Blood Cells and Tocopherol Deficiency in Infants and Children. Dr. Harold M. Nitowsky, Dr. Harry H. Gordon, and Dr. Marvin Cornblath, Baltimore.

Observations have been made of the hemolysis of erythrocytes in hydrogen peroxide according to the method of Gyorgy and Rose in the following groups of infants and children: unfed newborn, 235 term and 67 premature infants; thriving young term, 68, and premature, 137 infants; young infants admitted to hospital for acute illness, 33; malnourished infants and children with steatorrhea, 38, and without steatorrhea, 21; infants and children with a variety of less common metabolic and blood disorders, 27.

From 27% to 56% of unfed newborn infants in different categories showed over 50% hemolysis. No significant differences were found between full-term and premature infants, but the proportions of infants with over 50% hemolysis and the mean per cent hemolysis appeared to vary inversely with the economic status of the mother. Full-term infants fed cows' milk showed significantly less hemolysis at average age 7 weeks than at birth. Twelve of fourteen breast-fed infants showed virtually no hemolysis. On the other hand, premature infants fed partially skimmed cows' milk showed an increasing, or maintained, hemolysis with increasing duration of the low tocopherol diet. Full-term infants admitted to the hospital for illness and given low-fat diets showed over 50% hemolysis in two-thirds of the observations. In these premature and full-term infants, the administration of an emulsion of *d-l* alpha tocopheryl acetate in doses as low as less than 1 mg/kg. daily led to prompt reversal of the test.

Infants and children with steatorrhea (cystic fibrosis of the pancreas, celiac syndrome, biliary obstruction, familial steatorrhea) showed marked susceptibility of their red cells to H_2O_2. This could be reversed by feeding large doses of *d-l* alpha tocopheryl acetate or by in vitro addition of tocopherol to the incubation mixture. In the infants with biliary atresia, reversal of the test was particularly difficult.

None of the infants or children with the less common diseases (diabetes mellitus, two; hypoglycemia, one; galactosemia, one; cretinism, three; xanthomatosis, four; pseudohypertrophic muscular dystrophy, one; rheumatoid arthritis, one; "collagen disease," one; eczema, one;

chronic hepatitis, one; portal hypertension, one; leukemia, five; thalassemia, one; sickle-cell anemia, two; aplastic anemia, one; hemolytic anemia due to sulfonamide, one) showed significant hemolysis, except for one leukemic child on the day before death.

Studies are continuing of tocopherol levels and the mechanism of hemolysis.

Conclusions.—Using the hydrogen peroxide hemolysis test, evidence has been found of a mild degree of tocopherol deficiency in premature and full-term newborn infants. Its persistence is apparently related inversely to the tocopherol content of the diet, and it is easily reversed by the addition of tocopherol in amounts similar to that contained in breast milk. Because of the absence of clear clinical, physiological, biochemical, or pathological correlates, no conclusions have been reached concerning the desirability of supplementing the diet of artificially fed infants. In infants and children with steatorrhea the results of the hemolysis test indicate a more prolonged deficiency of tocopherol.

The Natural Course of Active Rheumatic Carditis with Special Reference to Evaluation of Hormone Therapy. Dr. May G. Wilson and Dr. Wan Ngo Lim, New York.

The effect of current therapy in the clinical course of active carditis is controversial. This is due in part to the paucity of data on the natural course of active carditis. To obtain information which would afford a basis for comparison with the effect of hormone therapy in active carditis, the following study was undertaken.

One hundred consecutive records of children under active supervision were obtained for analysis from the files of the Cardiac Rheumatic Clinic at The New York Hospital. In addition, 52 consecutive records of patients who recieved corticotropin (ACTH), cortisone, or hydrocortisone for an average period of seven days during 63 attacks of active carditis were similarly studied.

Preliminary analyses revealed that 100 children experienced 165 attacks of active carditis during 1930-1955. Of these, 72 were initial attacks and 93 were recurrent. The carditis was acute in 48 and subacute in 117 attacks. Routine symptomatic therapy included phenobarbital, acetylsalicylic acid, digitalis, and oxygen.

The following specific analyses were made: the duration and severity of active carditis in 165 patient attacks; a comparison of the incidence, severity, and duration of the symptoms and signs of active carditis in consecutive five-year periods from 1930 to 1955; relation of severity and duration of active carditis to the degree of residual cardiac chamber enlargement in initial and recurrent attacks.

The course of rheumatic carditis in patients receiving symptomatic therapy during the years 1930-1955 revealed no significant difference in the pattern of rheumatic fever over this 25-year period. During the follow-up of 3 months to 21 years (an average of 9 years), increasing cardiac chamber enlargement and the appearance of new murmurs rarely occurred in the absence of an overt attack of active carditis. The longer the duration of active carditis, the greater was the residual cardiac damage.

A comparison of the clinical course of patients receiving symptomatic and hormone therapy revealed striking differences both as to duration of active carditis and degree of cardiac damage sustained. It was found that the earlier the therapy, the shorter was the duration of active carditis and the less residual cardiac damage. In patients who were treated later than three weeks after onset, the duration of the disease was not infiuenced.

The natural course of active carditis for 165 patient attacks is presented. The data obtained proved useful in evaluating the effect of current therapy on the clinical course of active carditis and residual cardiac damage sustained.

Cirrhosis of the Liver in Infants and Children. Dr. John M. Craig, Dr. Sydney S. Gellis, and Dr. David Yi-Yung Hsia, Boston.

This study has covered all of the patients seen at the Children's Medical Center for a period of 30 years in whom a diagnosis of cirrhosis of the liver was made on a pathological as well as a clinical basis. These 98 patients thus represent about one-half of all of the patients seen wtih the clinical findings of cirrhosis. An attempt has been made to set up a classification of cirrhosis in infants and children on the basis of independent evaluations of the clinical history and of the pathological material. The results are summarized in the Table. Seven of the nine infants developing cirrhosis immediately subsequent to a typical episode of prolonged jaundice

after birth died from one month to four years three months later; two are still living, though one has evidence of advanced cirrhosis. The cirrhosis in these cases was rather diffuse without marked formation of regenerative nodules or massive atrophy.

The second group, of eight children, had typical episodes of epidemic viral hepatitis with positive liver function tests. This period of liver disease was followed by a quiescent period lasting from seven months to four years, only to be followed by recurrence of liver symptoms, ascites, and esophageal varices. Six of these patients have died. In this group the liver weights were below normal and the organs were grossly nodular. Microscopically the livers displayed a picture of postnecrotic scarring with regenerative nodule formation. Evidence of active hepatitis and an advancing cirrhosis was present in many.

The next group, of 13 children, had no known previous bout of clinical liver ailment. The onset of the cirrhotic symptoms was gradual and insidious. Eight of these patients died. Three patients have had splenorenal shunts for relief of their portal hypertension and are doing well. In the five autopsied cases the liver was enlarged, with moderate-sized liver nodules. Microscopically the lesion was that again of postnecrotic scarring. Active progression of the cirrhosis was present in 11 of the 13 cases.

Cirrhosis of the Liver in Infants and Children at the Children's Medical Center, Boston, 1924-1953

1. Cirrhosis associated with hepatitis		30
A. Neonatal hepatitis	9	
B. Viral hepatitis	8	
C. Without previous clinical development	13	
2. Obstructive cirrhosis		61
A. Biliary atresia	49	
B. Other obstructions to the extrahepatic bile ducts	5	
C. Fibrosis of pancreas	7	
3. Cirrhosis due to miscellaneous causes		7
A. Glycogen storage disease	2	
B. Galactosemia	2	
C. Cardiac cirrhosis	1	
D. Cholangitis	1	
E. Hemosiderosis	1	
Total		98

Forty-nine of the cases had atresia of the extrahepatic ducts. Thirty-nine died in the first year of life, while 5 lived to from 21 months to 5 years of age. Only in those surviving beyond 5 months of age did significant liver nodularity develop, and true regenerative nodules only after a two-year period of survival. Five children had other obstructions to the hepatic ducts, two with choledochol cysts, two with tumors, and one traumatic.

Seven children had focal obstructive biliary cirrhosis at autopsy, associated with fibrosis of the pancreas. Only one of these developed edema and ascites. Seven children developed cirrhosis secondary to a miscellaneous group of metabolic and physiological disturbances; none of these had portal obstructive symptoms.

Palpable Pyloric Tumors in the Early Days of Life. Dr. W. S. Craig, Leeds, England.

One hundred twenty newly born babies have been examined personally for evidence of a palpable tumor. In each case examination was carried out immediately after gastric lavage and during the time of a feed.

Of the 120 babies, 13 were selected for examination on account of persistent vomiting or regurgitation in association with unsatifactory weight progress. A contractile tumor was felt in 11 of the 13 cases. Of the 11 cases, 2 were operated on with satisfactory results. Symptoms in the remaining nine settled spontaneously, the tumors disappearing over varying periods of several months.

The remaining 107 babies were selected as being healthy and symptomless and because of their uneventful satisfactory progress. In 11 of the babies a clearly defined contractile tumor was palpated in the region of the pylorus, and in 11 others less clearly defined tumors were detected.

All findings were confirmed by an independent observer, and x-ray investigations were carried out in 40 cases. Each of the 120 infants has been followed up for a period of at least three months. The clinical findings and histories are compared with the detailed findings made personally on 125 cases of pyloric stenosis in babies operated on after the age of 4 weeks. The significance of a palpable contractile tumor in the first two weeks of life is discussed.

The Incidence of Abnormal Blood Levels of Lead in a Well-Baby Clinic Population, with Observations on the Value of Coproporphyrinuria as a Screening Test. Dr. J. Edmund Bradley, Dr. Albert E. Powell, Dr. William Niermann, Dr. Kathleen McGrady, and Emanuel Kaplan, Sc.D., Baltimore.

Freshly voided urine specimens (604) from 604 patients, age 6 to 60 months, of the Developmental Clinic of the University of Maryland were examined for coproporphyrin III by the de Langen and ten Berg method modified by McCord. Two hundred eight gave a coproporphyrinuria of 2+ or more. Three hundred ninety-six gave a negative test. Blood-lead levels and various other studies were done on all patients with 2+ or more coproporphyrinuria and on alternate patients with a negative test.

The mean blood-lead level as determined from 341 patients was 0.043 mg. per 100 cc. It was found that 28% showing coproporphyrinuria and 21% of those without had blood-lead concentrations of 0.06 mg. per 100 cc. or higher.

Correlations of blood lead concentration with a history of pica was as good as the correlation with coproporphyrinuria. Paint and plaster samples from the homes of patients with pica and who showed excessive blood lead revealed a high lead content.

A tentative conclusion which can be drawn from these data is that, at least in the case of patients coming from areas of old housing, a history of pica is of as much screening value in suggesting lead intoxication as is qualitative estimation of coproporphyrinuria. The incidence of excessive blood lead in apparently normal children of families in the lower urban income group is approximately one in four.

Studies on the Cardiovascular Dynamics in Children with Sickle-Cell Anemia. Dr. J. N. Etteldorf, C. P. Tharp, and M. D. Turner, Memphis.

Utilizing the dye dilution method (Evans Blue dye [T-1824]) adapted to a semicro scale the cardiac output, circulation time, plasma volume, and circulating erythrocyte mass were determined on nine children with sickle-cell anemia. A comparison with 13 normal children is shown in the tabulation below.

	S.-C. A. Children, Mean Values	Normal Children, Mean Values	Difference	Variation from Normal (1%)
Cardiac output, cc./min./kg.	268.80	150.81	117.99	—78.2
Cardiac index	6.49	3.72	2.77	+74.5
Plasma volume, cc./kg.	61.52	42.22	19.30	+45.7
Blood volume, cc./kg.	81.00	68.86	12.14	+ 9.0
Circulating erythrocyte mass, cc./kg.	19.5	26.7	7.20	—27.0
Circulation time, sec.	7.35	10.9	3.65	—33.5

The circulating hemoglobin mass (gm/kg/min.) and volume of erythrocytes (cc/kg/min.) per unit of time were calculated from the blood volumes, cardiac outputs, hemoglobin concentrations, and hematocrits for normal children and those with sickle-cell anemia. There was no significant difference in these values between the two groups. The circulating hemoglobin mass in the sickle-cell anemia patients was 20.1 gm/kg/min. and in the normal children, 18 gm/kg/min. The circulating erythrocytes volume in the sickle-cell anemia patients was 63.2 cc/kg/min., compared to 58.2 cc/kg/min. in normal children. This indicates that the marked increase in cardiac output (78.2%) was compensatory and in these children was sufficient to permit for adequate circulation of hemoglobin for oxygen transport. Atrioventricular oxygen differences (oxygen extractions) were not determined.

Data are being accumulated in children with other forms of chronic anemia and nutritional anemia and in adults with sickle-cell anemia in whom peripheral vascular changes are more advanced.

Oxygen of Dissociation of "Sickle-Cell" Blood. A. H. TUTTLE, DR. J. N. ETTELDORF, C. P. THARP, and M. D. TURNER, Memphis.

Specimens of whole blood from 21 children with sickle-cell disease and from 13 normal children were equilibrated for identical periods of time with six different mixtures of oxygen, carbon dioxide, and nitrogen. The oxygen tension ranged from 19.3 to 92.9 mm. Hg partial pressure. Carbon dioxide tension was constant in all mixtures. Each blood specimen was equilibrated three times with each gas mixture at 37 C and atmospheric pressure. Equilibration and subsequent analysis for oxygen content were carried out in the extraction chamber of a Van Slyke monometric gas analysis apparatus. The results were platted as "oxygen dissociation" curves.

Following equilibration at oxygen pressures of greater than 30 to 40 mm. Hg, "sickle-cell" erythrocytes were consistently, though insignificantly, less saturated than normal erythrocytes. Between 30 to 40 mm. Hg pressure, the "sickle-cell" curve shifts abruptly to the left of the normal curve. Subsequent experiments indicate that this abrupt shift is due to the presence of significant amounts of free hemoglobin released as a result of hemolysis of the "sickle" erythrocytes at low oxygen tensions. In contrast, hemolysis of erythrocytes in the normal blood specimens varied but little from the higher to lower oxygen tensions. A comparison of the degree of hemolysis produced by equilibration of blood with gas in tonometers with that produced by equilibration in the Van Slyke apparatus revealed that hemolysis occurred more readily in the specimens equilibrated in the tonometers.

From the results of these experiments we conclude that oxygen dissociation curves of erythrocytes with increased mechanical fragility cannot be correlated with curves obtained on normal adult erythrocytes until methods are applied in which the factor of hemolysis is eliminated.

The Renal Concentrating Defect in Sickle-Cell Anemia: A Reversible Complication of Sickle-Cell Disease. H. G. KEITEL and D. D. THOMPSON, Bethesda, Md.

Hospital records of 70 patients with sickle-cell anemia revealed 7 instances of urine specific gravities over 1.024, all in infancy. This suggested that the inability to concentrate urine is progressive and acquired early in life and may be reversible.

Five patients with sickle-cell anemia, whose hemoglobin contained 70%-85% 'S' hemoglobin, were studied. The maximum solute concentrations of urine in response to dehydration or vasopressin injection (Pitressin) was 540 mOsm. The immediate correction of anemia with normal cells resulted in little or no increase in ability to concentrate, whereas with continued transfusions the three youngest patients had a progressive increase in urine solute concentration reaching over 900 mOsm. in the two youngest patients.

The glomerular filtration rate and renal plasma flow, as measured by inulin and PAH, and the Tm_{PAH} were moderately elevated and were only slightly altered by transfusions.

The hospital recorded urine specific gravity of 14 patients with other types of anemia, and the urine concentration following dehydration in two patients with chronic hemoglobinemia and anemia showed no impairment in ability to concentrate urine.

It appears that the concentrating defect in sickle-cell anemia is progressive and in early life at least is reversible.

Appraisal of Respiratory Function in Newborn Infants. DR. HERBERT C. MILLER, DR. NED SMULL, and DR. EUGENE CONKLIN, Kansas City, Kan.

Detailed records were kept on the respiratory activity of over 75 premature infants and 25 healthy full-term infants. The latter served as controls. Analysis of these records showed that infants can be divided into three groups according to the behavior of their respiratory rates following birth. Group I consisted of infants who breathed approximately at 40 per minute beginning at birth and continued with very little fluctuation in the days following. Group II was composed of infants who breathed at high rates, usually 60 or over, during the first hour, but following this the respiratory rates declined, sometimes rapidly and sometimes slowly. Group III consisted of infants whose rates increased after the first hour from 25% to over 100% sometime during the next 24 hours. None of the infants in Groups I and II required any oxygen after the first few minutes, and all survived. All of the infants in Group III had sufficient respiratory distress as to require continuous oxygen. Over half of the infants in Group III died, death being related to a variety of postmortem findings. There was a greater tendency for premature infants to be in Group III than full-term infants, but not invariably. Serial measurements of

tidal and minute volumes as well as respiratory rates have been made on some of the infants. It has been concluded that the behavior of the respiratory rate during the first few days after birth is a good index of respiratory function and at the present time is the best clinical guide to oxygen therapy during the neonatal period.

The Incidence of Hypocalcemia on the First Day of Life in Mature and Premature Infants. Dr. I. F .Gittleman, Dr. J. B. Pincus, E. Schmerzler, B.S., and Dr. M. Saito, Brooklyn.

In the course of our studies on the serum calcium levels in infants during the first week of life we encountered 22 instances of hypocalcemia on the first day of life in a group of 838 infants. All of these infants were delivered per viae naturales. The mothers of 12 of the 22 infants with hypocalcemia suffered from disorders such as diabetes, placenta previa, abruptio placenta, "spotting" during pregnancy, and interia uteri.

Because of the high incidence of physiological disorders in the mothers of infants having hypocalcemia on the first day of life and since Caesarean sections are frequently performed because of diseased states in the mothers, we then studied the incidence of hypocalcemia on the first day of life in infants delivered by Caesarean Section. Seventy infants were thus studied, and fourteen of these had hypocalcemia on the first day of life, i. e., an incidence of 20% in the Caesarean-section babies as compared to 2.6% in the infants delivered per viae naturales. Seven of the fourteen hypocalcemic infants were born to mothers who had diabetes, placenta previa, preeclampsia, pyelonephritis, polyhydramnios, and inertia uteri.

Since in most of the cases of prematurity there are associated abnormal physiological processes in the mother, we investigated the incidence of hypocalcemia on the first day of life in premature infants. Forty-seven infants were studied. In 24 of these, hypocalcemia was present, i. e., an incidence of 51%. When these infants were grouped according to their birth weight we found, in Group I, consisting of 9 infants, whose weight varied between 1140 and 1470 gm., 8 instances of hypocalcemia, i. e., an incidence of 88.8%; in Group II, which comprised 13 infants, whose weight varied between 1620 and 1910 gm., 6 instances of hypocalcemia, an incidence of 46.2%, and in Group III, consisting of 25 infants, whose weight varied between 1920 and 2385 gm., 10 instances of hypocalcemia, an incidence of 40%.

The incidence of convulsions among the hypocalcemic infants was as follows:

1. In the 22 hypocalcemic infants in the group of full-term newborn infants studied we encountered 2 instances of convulsions.

2. In the Caesarean-section series, out of 14 infants with hypocalcemia, 3 had convulsions.

3. In the premature groups 3 of the hypocalcemic infants had convulsions, and these 3 were all in the lowest weight group.

In the 60 hyopcalcemic infants studied 8 developed convulsions.

We may therefore conclude that (1) hypocalcemia occurs on the first day of life in both mature and premature infants; (2) the hypocalcemic state was associated with manifest tetany in 8 out of 60 infants studied; (3) the incidence of hypocalcemia is highest in premature infants and increases in frequency as the weight of the infants decreases.

Study of Bilirubinemia of Prematures with Relation to Kernicterus. Dr. J. Robert MacLean, Dr. Jerold F. Lucey, and Dr. Ruth C. Harris, New York.

The relation of serum bilirubin levels to the development of kernicterus in premature infants is being studied. Observations on 60 infants in the weight range of 500-2000 gm. have been completed.

The literature to date contains very few observations of plasma bilirubin level in premature infants weighing less than 1500 gm. Our study will supply normal values in this weight range, which has included the majority of cases of kernicterus found in prematures in our 1954 experience.

Blood-group and Rh studies have failed to show evidence of maternal sensitization by the infant's erythrocytes.

The validity of the current findings and the correlation between serum bilirubin level and the degree of kernicterus in those infants who do not survive will be reported. Of the 60 infants, 20 have died. In 12 postmortem brain examinations there have been 4 instances of kernicterus.

The peak bilirubin concentrations of these kernicteric infants have been 15.2, 22.8, 13.2, 12.6 mg. per 100 ml. It would appear from the above figures that kernicterus can occur in nonerythroblastotic premature infants with bilirubin levels less than 20 mg. per 100 ml.

A remarkable drop in bilirubin levels immediately preceding death has been noted in several instances and is being investigated.

Observations on the Newer Tissue Culture Techniques in the Diagnosis and Study of Virus Infections of Children. Dr. A. J. Rhodes, Dr. A. J. Beale, and Frances Doane, B.Sc., Toronto, Canada.

The diagnosis and study of virus infections of children has been greatly facilitated by the introduction of the newer tissue-culture techniques. This presentation will describe the application of these methods to the study of some representative infections, with particular reference to the part that can be played by a virus research laboratory in a children's hospital.

Recent technical improvements have enabled such laboratories, almost for the first time, to identify viruses in pathological specimens within a short time. Viruses can be identified according to the nature of the cellular changes that they produce in tissue cultures, especially inclusion bodies, degenerative changes, and formation of giant cells. Such identification has been found of assistance in the laboratory diagnosis of many of the established virus diseases and in the study of the etiology of suspected virus infections.

A particular study has been made of the changes produced in epithelial cell tissue cultures infected by viruses. Trypsinized "monolayer" monkey kidney, human kidney, HeLa, and rabbit cornea cultures have been used. Cultures have been prepared on coverslips and stained at varying intervals after infection. In this way, the progression of cytologic changes has been followed in infections with poliomyelitis, herpes simplex, Coxsackie, "orphan," vaccinia, Western equine encephalitis, and other viruses.

1. *Uninfected Normal Tissue Cultures.*—A transmissible agent has been isolated from uninfected monkey-kidney cultures. It was first observed in monkey-kidney cultures maintained for 14 days and produces vacuolated multinucleate giant cells, with an intranuclear inclusion body. Similar changes, but without the intranuclear inclusion body, have been seen in many further monkey-kidney cultures. No such changes have been seen in human kidney, HeLa cell, or rabbit cornea cultures, though vacuolation of cells is common in cultures maintained for longer than 10 days.

2. *Poliomyelitis.*—It is possible by the rapid isolation and typing of poliomyelitis viruses in tissue cultures to add precision to the diagnosis of this disease. It is found that many cases of "nonparalytic poliomyelitis" are not infected with poliomyelitis virus. The pathological changes induced in monkey-kidney monolayers by poliomyelitis virus have also been studied. A large cytoplasmic inclusion body is formed. This body which contains mitochondria appears about six hours after infection.

3. *Coxsackie.*—A cytoplasmic inclusion body very similar to that observed in poliomyelitis infection has been seen in monkey-kidney cells infected with some strains of Coxsackie B virus. A similar body is also found after infection with a strain of "orphan" virus isolated from the cerebrospinal fluid. Many cases of "nonparalytic poliomyelitis" or aseptic meningitis yield Coxsackie viruses from the stools and show a rise in antibodies during infection. It is sometimes possible to clinch the diagnosis by the isolation of virus from the cerebrospinal fluid. So far eight strains, six Coxsackie B and two "orphan," viruses have been isolated from the cerebrospinal fluid of these cases.

4. *Herpes.*—Tissue cultures, especially of rabbit cornea, but also of HeLa cells and human kidney, have been found very useful in the study of herpetic infection. Typical intranuclear inclusion bodies appear in rabbit cornea cultures a few hours after infection and allow a rapid provisional diagnosis of infection with herpes simplex virus. The method has shown its value in the investigation of cases of stomatitis, keratitis, and Kaposi's varicelliform eruption.

Long-Term Study of Four Patients with the de Toni-Fanconi Syndrome with Emphasis on the Treatment of Electrolyte Deficiencies. Dr. Ruth C. Harris and Dr. Howard H. Mason, New York.

A classical example of cases described by de Toni, Fanconi, and also Debré has been followed for the past four and one-half years. A 26-month-old girl presented severe hypophosphatemic

rickets with multiple fractures and a large, firm liver. Urinary amino acid nitrogen output comprising approximately 24% of the total urinary nitrogen; glycosuria and phosphaturia were of high degree. During the period of observation no cystine deposits have appeared in her cornea, conjunctivae, or bone marrow. Rickets has been healed by large doses of vitamin D, and serum phosphorus levels have been maintained in the low normal range by the administration of 50 mEq. of phosphate per day. There has been a persistent hyperchloremic acidosis. Three years after onset of the disease serum potassium fell to very low levels. With the addition of 40-50 mEq. of potassium to the daily intake this has been corrected. With this addition of alkali there has been no decrease in the hyperchloremia. The amino-aciduria continues with urine alpha amino nitrogen output of 20%-27% of the total nitrogen.

Two brothers with cystinosis and renal changes have also been studied over several years. The older boy at the age of 2½ years presented symptoms of renal diabetes insipidus, while the younger at 17 months had rickets, amino-aciduria, glycosuria, and phosphaturia, as well as marked polyuria. He had a low glomerular filtration rate and has shown progressive nitrogen retention. Excessive water elimination and resulting large intake have been associated with recurrent episodes of vomiting in both patients. The older brother has shown persistently mild alkalosis with low serum chlorides, sodium, and potassium, which have been corrected by the addition of 4 gm. of sodium chloride and 2 gm. of potassium chloride to the daily diet. The younger boy has had hyperchloremic acidosis and nitrogen retention which has been benefited by intermittent administration of sodium bicarbonate. Both patients excrete approximately 3% of total urinary nitrogen as alpha amino nitrogen.

A fourth patient, with amino-aciduria, phosphaturia, and glycosuria, presents several features comparable to the patient described by Bickel as amino-aciduria in an obscure syndrome. This child has severe mental deficiency and hypermobility of both arms and legs.

Renal clearance studies have been performed on all these patients.

The Presence of Virus in Regional Lymph Nodes of Human Beings Attacked by Poliomyelitis: Remarks on Pathogenesis. Dr. Herbert A. Wenner and Paul Kamitsuka, Kansas City, Kan.

Previous work on the subject by one of us (H. A. W.) pointed to a widespread distribution of poliomyelitis virus in regional lymph nodes obtained from human beings succumbing to poliomyelitis. From the data, evidence was adduced (1951) that virus arrived at these way-stations as a consequence of transport in extraneural body milieu. One could not logically explain the presence of virus in separated regional lymph nodes except as a consequence of viremia and localization of virus in interstitial tissue spaces. From these compartments virus may be transported to lymph nodes where it can be found after the state of viremia.

In the earlier studies (1947 and 1951) the use of monkeys limited our observations. The study was reopened in 1954, using tissue culture methods. At the present time, studies have been made on 15 patients. Virus was detected in the central nervous system of all and in regional lymph nodes of 13 of the 15 human beings. Poliomyelitis virus was not isolated from the blood, liver, pancreas, or mesenteric fat obtained from patients after death.

Detection of virus from regional lymph nodes is more readily made in patients whose death occurred within five days after onset of illness. The titer of detectable virus in lymph nodes is low, suggesting that it is transported to those loci rather than multiplying in them. Comparative antibody titers in serums and lymph nodes are incompletely studied, but will yield valuable information from which further interpretation will be forthcoming.

Delayed Cystography in Recurrent Urinary Tract Infections in Girls. Dr. Bertram R. Girdany and Dr. S. H. Johnson III, Pittsburgh.

Routine excretory and retrograde urographic studies and cystoscopic examination often fail to disclose the anatomic change responsible for recurrent urinary tract infection in girls. The relationship between these infections and lymphatic drainage or bacterial emboli is vague and unsatisfactorily defined.

Incompetent ureterovesicle valve mechanisms allow retrograde flow of bacteria-containing urine from the bladder and may provide the basis for upper urinary tract infection. Serial roentgenograms of the abdomen following installation of opaque medium into the bladder demonstrate retrograde flow of the medium into the upper urinary tract. Increasing intravesicular

pressure produces progressive dilatation of the ureters and renal pelves. These changes may be present despite apparently normal routine urographic and cystoscopic studies.

Retrograde flow of urine from the bladder in girls with inadequate ureterovesical barriers occurs in the presence of increased intravesicular pressure. Enforced urinary retention at school, at double-feature movies, and during long automobile trips causes such increased pressure.

This paper discusses the technique of, indications for, and the authors' experience with delayed cystography in girls with recurrent pyuria and in normal controls. Appropriate treatment in selected cases is suggested.

The Development of Tyrosine Oxidase Activity in Liver. Dr. Norman Kretchmer, Helen McNamara, M.A., Dr. Henry L. Barnett, and Dr. S. Z. Levine, New York.

The authors observed the excretion of abnormal quantities of tyrosine and *p*-hydroxyphenylpyruvic acid (*p*-OHPP) in the urine of premature infants receiving diets high in protein without added ascorbic acid. The amino acid tyrosine is normally oxidized by the tyrosine oxidase system via a series of steps to acetoacetate and fumarate. The first obligatory reaction in this oxidation is the nonoxidative transamination of tyrosine to its keto analogue, *p*-OHPP, and the subsequent oxidative steps start with this compound. Absence or inactivity of the enzymes necessary to transaminate tyrosine or to oxidize *p*-OHPP could explain the accumulation and excretion of these substances.

In order to test this hypothesis, the livers from young premature infants (4 to 168 hours old) and from adults were obtained at autopsy, and the tyrosine oxidase activity of the homogenates was determined manometrically in a Warburg apparatus. As a control for the human material, tyrosine oxidase activity was similarly determined in liver of fetal, newborn, infant, and adult rats. Ascorbic acid was added in all manometric determinations on the perinatal homogenates in amounts (500γ) previously found to stimulate maximally oxidative activity in adult liver. Besides measuring oxygen uptake, the concentrations of tyrosine and *p*-OHPP were estimated colorimetrically before and after incubation.

The results indicated that tyrosine oxidase activity of adult liver homogenates was increased tenfold or more above that of young premature infants and of fetal liver, irrespective of the standard of reference used for oxygen consumption, i. e., concentrations of hepatic nitrogen, phosphorus, or deoxyribonucleic acid; wet weight of liver; total body weight, or surface area. With the homogenates from young premature infants there was a concomitant in vitro accumulation of *p*-OHPP and a proportionate decrease in tyrosine utilization after incubation. The addition of ascorbic acid had no effect on the oxygen consumption of homogenates of liver of the young premature infants or of the fetal rats. This result contrasts with the marked effect of ascorbic acid on the tyrosyluria previously found in older premature infants.

The above results indicate that the absent or slight oxidative activity found with the homogenates of liver from young premaure infants is due not to a decrease in transamination, but rather to a lessened or absent oxidative activity not dependent on ascorbic acid in the quantities used. These data suggest that the oxidative activity of the tyrosine oxidase system is dependent upon intrinsic biochemical development of the liver and that it develops only after transaminase activity is already demonstrable.

If these in vitro observations hold for the living organism, and induced tyrosyluria in young premature infants should not be abolished by ascorbic acid as it is in older premature infants. This possibility awaits further study.

The Risk of Poliomyelitis Infection Among Exposed Hospital Personnel. Dr. P. F. Wehrle, Baltimore.

The presence of poliomyelitis virus in the throat secretions and stools of patients in the early stages of poliomyelitis infection has been demonstrated repeatedly. The persistence of virus in the stools during early convalescence has also been well documented. These findings would appear to suggest that persons engaged in the care of poliomyelitis patients may be exposed to an increased risk of infection with this agent.

The present study is based on a serological survey of 50 student nurses, nurses, and house officers working on the acute poliomyelitis service of the Baltimore City Hospitals. An additional group of 25 persons working on other services in the same hospital was selected for control purposes. Sera were obtained in June and early July of 1954 and in November and December of 1954. During this interval a total of 128 patients with poliomyelitis were admitted, 84 on

the pediatric service (including children to age 14 years) and 44 on the medical service. Paralysis was demonstrated in 63% of these patients. Approximately two-thirds of the cases from whom virus was isolated represented Type I poliomyelitis virus infections, and the remainder Type III infections.

Neutralization tests in trypsinized monkey-kidney tissue cultures at twofold serum dilutions from 1 : 4 to 1 : 4000 were done on paired sera from hospital personnel. The three types of poliomyelitis virus were used in doses of from 32 to 100 T. C. I. D_{50}.

Of the hospital personnel tested, 24% were negative (titer less than 1 : 4) for Type I neutralizing antibody, 17% negative for Type II antibody and 32% negative for Type III antibody on the initial sera. In personnel without serological evidence of previous Type I, II, or III infection, working on the polio ward, there was a minimum of 47, 36, and 53 person-weeks of contact experience with acute cases.

In addition to those persons without demonstrable neutralizing antibody, a second group had antibody present in low titer against one or more strains. Type I antibody was present at this low level in 20% of the personnel, and Type II and Type III antibody titers were present in 16% and 19%, respectively.

In none of the hospital personnel was evidence of infection noted during the 1954 season, as measured by a rise of greater than fourfold in neutralizing antibody titer. In addition to the lack of definite serological evidence of infection, it was apparent that the frequent twofold and rare fourfold variations in titer were distributed in a random pattern regardles of exposure, service, or occurrence of minor illness.

It is apparent that the experience in this study is markedly different from the high proportion of infections noted in family groups. This difference is believed to be due primarily to techniques of medical asepsis as used in the hospital and, secondly, to a lesser degree of infectiousness of the patient during hospitalization as compared with the prodromal period.

Agammaglobulinemia: II. An Experimental Study. DR. ROBERT A. GOOD, Minneapolis.

Last year we described initial efforts to interpret the experiment of nature represented by the patients with agammaglobulinemia. During the past year we have studied eight cases of this disease and extended the experimental observations.

Two patients were adults suffering from acquired agammaglobulinemia, whereas six were children with the congenital disease. Experimental studies have established the following points:

1. Hepatic function, blood coagulation, and protein formation, except for gamma globulin, are normal in these patients.

2. Gamma globulin is not destroyed more rapidly than normal in these cases.

3. All of these patients have a profound immunological handicap. This has been defined as an "immunological paralysis" in four and "immunological paresis" in four.

4. Hematological disturbances, including various forms of neutropenia, eosinopenia, lymphopenia, reticulum hyperplasia, and thymic tumor, have been observed. The common denominator of all these abnormalities and their link to agammaglobulinemia and failure of antibody production is thought to reside in the reticulum and be expressed morphologically as failure of plasma cell formation in response to intensive antigenic stimulation.

5. Agammaglobulinemic patients produce acute-phase reactants including C-reactive protein, mucoprotein, fibrinogen, and heparin-precipitable protein as well as do normal persons. Their reaction to Gram-negative bacterial endotoxins is also similar to that of normal subjects.

Agammaglobulinemic patients appear to be deficient in capacity to develop bacterial type hyper-reactivity and atopic or reagenic type hypersensitivity. However, transmission of bacterial type hypersensitivity against tuberculin and streptococcal products by the injection of white cells from sensitive donors was successful. Atopic reactivity to skin-test antigens was passively transferred to one of these patients by intradermal injection of serum from a sensitive donor.

Homotransplantation of skin from unrelated persons has been successful in two agammaglobulinemic children, and prolonged survival (three and one-half months) occurred in a hypogammaglobulinemic adult. Transplantation of skin from agammaglobulinemic subjects to normal persons uniformly failed, the rejection being associated with plasmacytosis in the skin and regional lymph node. These observations strengthen the concept that homotransplantation failure has an immunological basis.

Production of antibody occurred in an agammaglobulinemic patient following homotransplantation of lymph nodes from a sensitized normal person. After two months the nodes sloughed and the immunological responsiveness disappeared. Lymph nodes have also been transplanted to an agammaglobulinemic child who is at present receiving antigenic stimulation.

Finally, a woman having acquired agammaglobulinemia was studied during and subsequent to her pregnancy. Whereas prior to pregnancy and during the first trimester she failed to respond to antigenic stimulation, a significant response occurred during the last 30 days of the pregnancy. After delivery of fetus and placenta, the immune response in the mother was no longer demonstrable. Electrophoretically determinable gamma globulin remained absent throughout the pregnancy, and the child was agammaglobulinemic during the first two months of life. During the third postnatal month the baby began to produce gamma globulin, to make antibody, and to show plasma cells in the stimulated reticuloendothelial tissues. The observations are interpreted as evidence for the plasma-cell theory of antibody production and as an indication that the placenta may be a site of antibody formation.

Summary.—Extensive studies designed to interpret the fascinating experiment of nature posed by the immunological deficit associated with agammaglobulinemia in eight patients have been described.

Splenomegaly in Sickle-Cell Anemia. Dr. R. Janet Watson, New York.

Of 115 patients with sickle-cell anemia, 21, ranging from 1 to 54 years of age, had palpable spleens. Splenomegaly was found in 33% of patients in the first 10 years of life and in only 10% of those older. In six children and one adult the enlargement of the spleen was transient.

There was a rough correlation between the size of the spleen and the severity of the anemia. Six of the twenty-one patients with splenomegaly had unusually large spleens in association with a high transfusion requirement and an unusually severe anemia. Their average hemoglobin was 4 to 5 gm. per 100 cc., in contrast to an average of 8.5 gm. in those patients without splenomegaly. In two patients, 10 and 11 years of age, spleens weighing 1300 and 750 gm., respectively, were removed. Normal transfused blood had a half-life of only 7 and 14 days, respectively, before splenectomy and had a normal survival after splenectomy. These findings indicated hypersplenism, i. e., a superimposed extracorpuscular defect. Both patients have maintained a greatly improved clinical and hematological status for two years postoperatively without requiring any transfusions.

Studies at operation in one case showed a much higher number of circulating cells in the reversible sickled shape in the splenic vein and pulp than in the femoral artery. Furthermore, cells in the irreversible sickle shape were concentrated in the splenic pulp as high as sixty-fourfold in comparison with those in the peripheral blood. Splenic aspirations were performed in seven other cases with splenomegaly, and similar results were obtained.

Carcinoma of the Thyroid Gland in Children. Dr. Alvin B. Hayles, Dr. Roger L. J. Kennedy, Dr. Oliver H. Beahrs, and Dr. Lewis B. Woolner, Rochester, Minn.

This paper will appear in a forthcoming issue of the A. M. A. American Journal of Diseases of Children.

Adequacy of Blood Flow Through By-Pass of the Right Heart and Its Application to the Surgery of Congenital Heart Disease. Dr. Paul R. Lurie, Dr. Angelo Riberi, Dr. Warren E. Coggeshall, Dr. Roy H. Behnke, Dr. Hisashi Kajikuri, and Dr. Harris B. Shumacker Jr., Indianapolis.

Others have shown that the right ventricle is at least to some extent nonessential in the normal dog. The present work was done to compare blood flow developed in the same dog with and without the pumping action of the right heart.

In dogs, the superior vena cava was anastomosed end-to-end with the right pulmonary artery, so that systemic venous blood could flow directly into the right lung without the propulsion of the right heart, while the left lung retained its normal circulatory connections.

The procedure was well tolerated. The dogs showed some increased dilatation of the neck veins, but no evidence of subcutaneous or cerebral edema and no impairment of exercise tolerance while running outdoors or on the treadmill.

Catheterizations were performed at intervals varying from 7 to 40 days after operation. A catheter was passed from a neck vein into the right pulmonary artery and another from below via the right heart into the left pulmonary artery. The pressures in the superior vena cava near

the heart averaged 7.8 cm. higher than those in the inferior vena cava. Blood oxygen saturation averaged 65% in the right pulmonary artery and 60% in the left pulmonary artery. Arterial blood was usually fully saturated with oxygen. While the catheter was in the branch pulmonary artery the cyanide circulation time was measured from the tip of the catheter to the carotid sinus. Right pulmonary time averaged 5.7 sec., left 4.8 sec. At other times the gas exchange from each lung was determined. The right lung consumed an average of 44 cc/min., the left 104 cc/min.

In open-chest dogs, direct blood-flow measurements were made with a rotameter incorporated in the right heart by-pass. At times the superior-vena-cava-to-right-pulmonary-artery flow was as high as the control superior-vena-cava-to-right-auricle flow.

All methods demonstrated that physiologically adequate flows from the drainage area of the superior vena cava occurred without the work of the right heart.

Studies of the adequacy of the total caval blood flow without right heart work are in progress.

These studies are applicable to the surgery of congenital heart disease. In patients with large left-to-right shunts with low pulmonary resistance, perfusion of the lungs with pure systemic blood at systemic venous pressure, while resulting in greatly lowered total pulmonary blood flow, might be expected to cause little reduction of effective pulmonary blood flow, i. e., the flow of systemic venous blood to the lungs. Certain cases of transposition of the great vessels, common truncus arteriosus, common atrioventricular canal, large ventricular septal defect, and aortic-pulmonary septal defect would fall into this potentially operable group.

A few operative applications of these principles to desperately ill patients have been made with no survivals beyond a few hours but encouraging immediate results.

Benign Pharyngeal Erythema and Follicle Formation in the Newborn. Dr. Alfred L. Florman and Dr. Moises Bergher, Manhasset, N. Y.

Our attention has recently been directed to a lesion in the pharnyx of newborn infants. It characteristically consists of several small 1 to 2 mm. white or yellow follicles on an erythematous base. These are usually found on the anterior tonsillar pillars (glossopalatine arches) on the second or third day of life. Occasionally the follicles are replaced by shallow ulcers. The condition appears to be benign and clears in two to four days. Von Reuss described a somewhat similar condition under the name "spots on the palate."

During the four-month period from October, 1954, through January, 1955, these lesions were found in the throats of 78 infants. This represented approximately 20% of all the full-term babies delivered at the North Shore Hospital. More than twice as many instances were seen during December as during October—31 as compared to 14. Nevertheless the numbers of infants discharged from the nursery in those months were similar—99 and 91.

Preliminary bacteriological and virological studies have failed to reveal an etiologic agent. (The virology studies were carried out with the cooperation of Dr. Walter Henle and Miss Helen Zepp of the Mount Sinai Hospital.) The possibility of the trauma of postdelivery pharyngeal suction being the cause was considered and eliminated. It could be shown that the lesions occasionally appeared in infants who were never suctioned and were not found in some babies who had received a great deal of suction. Pharyngeal smears from infants with lesions showed many squamous cells and a characteristic cluster arrangement of what appeared to be epithelial cells from deeper layers. There was a striking absence of inflammatory cells. These smears therefore serve to differentiate further this benign pharyngeal condition from potentially more serious bacterial infections. The smears have also suggested the possibility that these pharyngeal lesions may represent an effect of estrogen withdrawal. Studies directed at the etiology of this condition are still in progress.

On the Nature of Fibrinoid Degeneration in the Collagen Diseases. Dr. David Gitlin and Dr. John M. Craig, Boston.

The pathogenesis of the group of disorders collectively termed "collagen diseases" is still unknown. Although these diseases have been attributed to a number of causes, from specific infection to an antigen-antibody reaction, it is generally accepted that the pathological lesions are characterized by fibrinoid degeneration of collagen.

Using fluorescent antibodies as specific histochemical reagents, it is possible to study the nature of the lesions seen in rheumatoid arthritis, disseminated lupus erythematosus, periarteritis,

dermatomyositis, glomerulonephritis, and related disorders. It can be demonstrated that the fibrinoid material seen in these lesions is actually fibrin and that it does not represent any stage of collagenous degeneration. Although these findings do not settle the etiology of these diseases, the evidence indicates that the lesions studied are inflammatory rather than degenerative in nature.

It would appear that these disorders are not diseases of collagen per se but rather diseases in which the characteristic inflammatory lesions are most readily seen in the connective tissues of various organs.

A New Syndrome Associated with Congenital Heart Disease. Dr. R. E. Bonham-Carter, London, England.

The syndrome consists of facies with wide-set eyes, square, box-like chests, enlargement of the liver and spleen, and a mottled skin, and the types of congenital heart disease with which this syndrome is most usually associated are endocardial fibroelastosis and pulmonary stenosis including Fallot's tetralogy. The presence of endocardial fibroelastosis has been confirmed when predicted by postmortem material and by left auricular biopsy when the thoracotomy has been done.

Low Birth Weight in Cystic Fibrosis of the Pancreas. Dr. Paul H. Boyer, New York.

Many of the patients with cystic fibrosis of the pancreas have a low birth weight. In several families it was observed that the offspring with pancreatic fibrosis weighed less at birth than did their unaffected siblings, regardless of birth order.

The mean birth weights of 75 white girls and of 98 white boys with cystic fibrosis of the pancreas were compared with the mean birth weights of a control girl and boy population. Controls were 502 white girls and 498 white boys born in Sloane Hospital for Women. This control group, taken as a whole, is believed to be more comparable to the test group in ethnic composition and in social, economic, and hygienic background than any other reference population we could find.

The mean birth weight for children with cystic fibrosis of the pancreas was less than the calculated control mean value for the corresponding sex. The difference between the mean values was 299 gm. for the girls and 241 gm. for the boys. These differences are more than four times the value of the standard error of the difference for each group. It is unlikely that differences of this magnitude would occur by mere chance.

Only 48% of the boys with cystic fibrosis of the pancreas had a birth weight above 3000 gm. The percentage for the control male population was 77.7%. For the baby girls with cystic fibrosis of the pancreas the percentage with birth weight above 3000 gm. was 42%, as compared with 70.3% for the control female population.

This difference in birth weight between patients with cystic fibrosis of the pancreas and a normal population favors the hypothesis of a metabolic defect which affects fetal growth in some way. It may be that the mother fails to provide the fetus with some factor essential for its normal development or that the fetus, on account of some inherited metabolic defect, is unable to utilize the nutritional elements provided by the mother.

In a recent experiment conducted by Dr. Dorothy H. Andersen it was attempted to modify the incidence of cystic fibrosis of the pancreas by means of a superior diet during pregnancy. One hundred women who had had at least one other pregnancy resulting in a child with cystic fibrosis of the pancreas were instructed to take a diet rich in protein, vitamins, and minerals and providing 2500 to 2800 Calories daily.

The higher birth weight of the infants, both unaffected and those with cystic fibrosis of the pancreas, born to the mothers who had followed this dietary advice during pregnancy is in accordance with the known fact that a high-protein diet during pregnancy will result in a heavier infant. The fact that the birth weight and perhaps the incidence of the disease may be modified by a good pregnancy diet is a point that deserves further study.

Studies on Glycogen-Storage Disease Phosphorylated Intermediates in the Peripheral Blood. Dr. Richard Wagner, Boston.

In a 7½-month-old child with glycogen-storage disease (fasting blood sugar 15 mg. per 100 cc., serum glycogen 19 mg. per 100 cc.) the reducing substance in the peripheral blood was isolated as an unfermentable barium-soluble, alcohol-insoluble fraction of a trichloroacetic acid

filtrate of whole blood. The reducing value in terms of glucose amounted to 9.5 mg. per 100 cc. of blood. When incubated with a phosphatase at pH 8.7, eighty-four per cent of the organic phosphorus was liberated as inorganic phosphorus. During the incubation the reducing power increased by 41%. Inorganic phosphorus could be liberated on incubation with a liver phosphatase not only from the isolated fraction, but also from whole blood. Its order of magnitude exceeds that in blood from normal individuals by several hundred per cent. In another child (5 years old, fasting serum sugar 8.56 mg. per 100 cc., serum glycogen 39.6 mg. per 100 cc.) a similar reducing fraction with extremely high phosphorus in organic linkage could be isolated. The phosphorylated intermediates were identified by filter-paper chromatography on sulfuric-acid-tungstate filtrates of the serum. In most instances the reducing fraction value of the specimens coincided with that of glucose 6-phosphate; occasionally with that of fructose 6-phosphate; in one instance with that of hexose 1, 6-diphosphate, but in all instances the reducing fraction value of the patients' material was below that of normal control specimens which were above the standards. The Seliwanoff reaction in the tungstate filtrate of the serum was strongly positive. Separation of the sugar phosphates by ion exchange with the use of the borate complex is in progress.

The liberation of inorganic phosphorus and the increase of the reducing value on incubation with a phosphatase as well as the results of chromotography are considered a satisfactory proof for the presence in the blood of phosphorylated intermediates of the glycolytic cycle in glycogen-storage disease.

Conclnusions.—The presence of sugar phosphates in the blood of patients with glycogen-storage disease explains some of the peculiarities of this enzymatic defect. The low reducing value of the blood is not only the result of the absence of glucose, but also of the presence of sugar phosphates of lower reducing power than that of glucose. Glucose 6- and fructose 6-phosphate are unable to penetrate the cell membrane, in contrast to glucose. This may be one of the factors responsible for the retarded physical development in the carriers of the defect.

Inhibition of Citraturia by Acetazoleamide (Diamox) and the Production of Nephrocalcinosis. Dr. Harold E. Harrison and Dr. Helen C. Harrison, Baltimore.

The urinary excretion of citrate under normal physiological conditions varies with the cation-to-anion ratio in the urine. The excretion of citrate increases as urine pH is increased by administration of alkalinizing salts. Vitamin D also exerts an effect upon urinary excretion of citrate. Urinary citrate is reduced in the vitamin-D-deficient subject and is increased by the giving of vitamin D. Experimentally, marked variations in the urinary output of citrate can be produced by differences in the vitamin D content and the acid-base ratio of the diet.

The administration of acetazoleamide to rats was found to reduce the urinary excretion of citrate to very low levels and to inhibit the augmenting effect of alkalinization and of vitamin D upon citraturia. This reduction of urinary cirtate levels by acetazoleamide was utilized to study the role of citrate in the stablization of urine calcium and in the prevention of precipitation of calcium salts in the urinary tract. The inhibition of citraturia by acetazoleamide was not accompanied by proportionate decrease in the urinary excretion of calcium and phosphorus. Under certain experimental conditions the administration of acetazoleamide to rats was associated with the precipitation of calcium phosphate in the renal tubules or the formation of renal calculi in the calyces. The occurrence of renal calcinosis or of calculus formation was depenedent upon the composition of the diet.

If the diet was high in calcium and phosphorus, addition of acetazoleamide caused renal calcinosis with precipitation of calcium phosphate in the loops of Henle. If the diet was calcium-rich but low in phosphorus renal calculi were formed in the calyces adherent to calcified plaques beneath the epithelium of the papilla.

Since marked reduction of urinary citrate excretion has also been found in a patient with renal tubular acidosis, the occurrence of renal calcinosis in this syndrome may be on the same basis as that found in the animals given acetazoleamide.

These studies indicate that urine cirtate is of importance in the prevention of calcium precipitation in the urinary tract. They also suggest that the effect of acetazoleamide on renal tubular handling of citrate is exerted in the proximal portion of the tubule.

The Biosynthesis of Purines in Chick Embryos with Experimental Porphyria. Dr. Robert A. Aldrich, Dr. Ellen L. Talman, and Dr. Robert F. Labbe, Portland, Ore.

Experimental porphyria can be induced in chick embryos by injecting Sedormid (allylisopropylacetylcarbamide) into the yolk sac (*J. Biol. Chem.* **212**:663, 1955). We have previously reported that growth failure and congenital malformations of the feet, beak, and feathers may occur in association with this disturbance in porphyrin metabolism (A. M. A. Am. J. Dis. Child. **88**:514, 1954). During these experiments it was noted that uric acid excretion was reduced in treated chicks at a time when porphyrin content of the allantoic fluid was rapidly increasing (*Biochim et biophys. acta* **15**:590, 1954). This reciprocal relationship between purine and porphyrin excretion may have fundamental significance in explaining some of the above effects. A known link between purine and porphyrin biosynthesis is the common precursor derived from succinate and aminoacetic acid, namely, Δ-aminolevulinic acid (*J. Am. Chem. Soc.* **75**:4873, 1953). This fact points toward the anabolic rather than the catabolic pathway as a probable site for the metabolic defect. New experimental evidence supporting this viewpoint will be presented in detail and is summarized below.

1. Adenine (5 mg.) was injected into the yolk sacs of control and Sedormid-treated 8-day-old chick embryos. Increased uric acid excretion into the allantoic fluids resulting from catabolism of the exogenous purine was compared, and no significant difference in the oxidative catabolism of adenine was observed. This finding strongly suggests that the catabolic-excretory mechanism for purines is not impaired in experimental porphyria.

2. Alpha C^{14}-labeled aminoacetic acid was administered intravenously to Sedormid-treated and control chick embryos and the incorporation of isotope into uric acid measured. In two separate experiments the incorporation of isotope (total radioactivity) was reduced by 58% and 34% in the porphyric embryos. Since several positions in the purine nucleus are derived from aminoacetic acid, this experiment indicates that purine biosynthesis is probably inhibited by Sedormid.

3. Exogenous adenine was injected into the yolk sacs of Sedormid-treated and control chick embryos, and concentrations of porphyrins appearing in the allantoic fluid were measured over a period of several days. Adenine treatment of porphyric embryos produces a marked reduction in porphyrin excretion. These data further illustrate the reciprocal behavior of porphyrins and purines under our experimental conditions. In this instance provision of the exogenous adenine presumably reduces the stimulus to homeostatic mechanism driving the succinate-aminoacetic acid cycle, thus reducing porphyrin formation.

The hypothesis that Sedormid inhibits purine biosynthesis by affecting the succinate-aminoacetic acid cycle is strengthened by these data. Such an event is most likely to occur during the oxidative deamination of Δ-aminolevulinic acid.

Exchangeable Sodium of Bone in Young and Old Animals. Dr. Gilbert B. Forbes, George Mizner, and Anne Lewis, Rochester, N. Y.

Several studies are already reported in the literaure on the extent of radiosodium exchange in the skeletal tissues of man and animals. There is general agreement that such exchange in the adult organism includes only about a third of the total sodium present in bone.

The present experiments were designed to compare radiosodium exchange in young and in adult animals. Radiosodium (Na^{22}) was injected intraperitoneally, and after a period of time the specific activity of the plasma and bone sodium determined (the latter by a new method developed in our laboratory). Two groups of rats were studied: one group was 17-21 days of age; the other, adults averaging 275 gm. in weight. The sodium and radiosodium content of bone were corrected for "extracellular" Na on the basis of chloride content, and the remainder designated as "extra" sodium. Values for the infant rats were corrected for the amount of skeletal growth presumed to have occurred during the equilibration period.

The results indicate a marked difference in the degree of exchangeability of skeletal sodium for the two groups. After a 24-hour equilibration period, approximately 30% of the "extra" Na was found to have exchanged in the adult, whereas the value for the infant group was about 60%.

On the basis of these results it can be concluded that skeletal sodium in the infant animal is much more readily available than that of the adult for general metabolic purposes. The implica-

tions of a study of this sort depend upon a knowledge of the magnitude of the skeletal depot of sodium. To this end, data on total body sodium in man as determined by isotopic dilution and by carcass analysis will be presented, together with new information on skeletal sodium content.

Influence of Protein Level and Infant Formula Preparations on Growth and Reproduction in Rats. DR. WARREN M. COX JR., ARTHUR J. MUELLER, B.S., and DR. R. C. ELLINGSON, Evansville, Ind.

The occurrence in recent years of megaloblastic anemia and pyridoxine deficiency in infants after feeding modified milk formulas has directed attention to the need for more complete nutritional evaluation of such foods. The rat is not the ideal animal for this purpose, since unmodified human milk does not support rat growth. Part of the failure of the rat to grow may be due to the high requirement for calcium and phosphorus and the relatively small amount of these minerals in human milk. High levels of lactose, as in human milk, are not well tolerated by the rat, but growth is almost satisfactory if other dietary essentials are supplied. We have therefore felt justified in using this useful animal in the assay of foods for infants. The data submitted are preliminary and relate to only one nutritional essential of such products—their protein content.

Five formula products have been studied in comparison with seven synthetic diets containing protein (casein and lactalbumin) at levels from 5% to 40% as controls. Vitamins and minerals were added to each diet in amounts adequate to supply the requirements for growth and reproduction. A total of 180 weanling rats and 2400 of their young have been studied. The gain in weight on synthetic diets increased as the protein level increased to 20% of the diet, but the gain on formula products was always less than the gain on synthetic diets providing the same protein intake. Weight gain when formula products were fed paralleled their protein content. Food and caloric intake was greater with the low-proten diets and low-protein formula products than with the higher protein diets. Water intake varied greatly and was related in part to the level of nitrogen in the diet and in part to the lactose content.

Carcass analyses of the young from mothers raised on the 12 diets showed that the total protein, fat, and ash contents were proportional to the protein intake of the lactating mothers except for two of the formula products studied. The per cent body composition of the carcass was not affected by the level of protein in the diet. The weight change of the lactating females was related directly to their protein intake, with those eating less than 4.0 gm. daily losing weight. Food intake was not increased to compensate for lower protein levels, presumably because of gastric capacity. Reproduction was poor on 5% protein diets, and at intermediate levels the young were small in size. The weight gain of the nursling young of three generations was constant on the same diet.

Summary.—Protein levels in infant formula products account for wide differences in the weight of rats raised on these products. The protein efficiency of all formula products studied was less than that of a purified mixture of casein and lactalbumin, suggesting the importance of careful studies of the effect of manufacturing techniques on nutritive quality.

Hypoproteinemia in the Nephrotic Syndrome: Metabolism of Specific Plasma Proteins in Different Stages of the Disease. DR. DAVID GITLIN, DR. CHARLES A. JANEWAY, and DR. LEE E. FARR, Boston.

Six children in different stages of the nephrotic syndrome were given tracer doses of radioiodinated human plasma albumin and radioiodinated human plasma γ-globulin intravenously in sequence. In three of these children a subsequent intravenous injection of radioiodinated human iron-binding globulin was given. The disappearance of each specific radioiodinated plasma protein from the circulation was studied as well as the cumulative appearance in the urine of radioiodinated protein and of non-protein-bound radioiodine. Concentrations of total albumin, γ-globulin, and iron-binding globulin in serum, urine, and edema fluid were estimated immunochemically, and renal clearance of these proteins was determined from these measurements.

It was found that the deficiency of circulating albumin, γ-globulin, or iron-binding globulin in children with the nephrotic syndrome is due to an increased rate of catabolism of the proteins in addition to the large urinary loss. The rate of synthesis of albumin or iron-binding globulin appears to be within normal limits, while that of γ-globulin may be normal or somewhat increased. In the stage characterized by considerable hypoalbuminemia without apparent ascites

but with minimal edema, hypoproteinemia may be associated with either a greatly increased rate of catabolism of albumin or a severe degree of albuminuria. However, severe hypoalbuminemia in the full-blown active stage of disease with ascites and anasarca is the result of the simultaneous occurrence of both greatly increased catabolism and alubuminuria. In a patient with the nephrotic syndrome but in complete remission the catabolic rate of the proteins was normal and proteinuria was greatly diminished.

A method for mathematical analysis of renal clearance of these specific proteins had to be devised for calculation of the data. Analysis in a conventional manner indicated that the 50% turnover rate for endogenous plasma protein could not be estimated from the plasma disappearance curve of its radioiodinated homologue in edematous patients, due to failure of the labeled protein used as a tracer to attain equilibrium between vascular and extravascular fluids. In the phase of exponential disappearance from the circulation, the specific radioactivity of the labelled protein in the extravascular fluid might be as high as 8 to 30 times that in the plasma, because the labelled protein was being excreted in the urine and catabolized at a more rapid rate than it could be replaced from the extravascular compartment. The large apparent body pool of albumin indicated by extrapolation of the exponential portion of the curve reflected this difference in specific activity and thus indicated the actual volume of distribution of the injected radioiodinated plasma protein tracer during this phase, but not of the endogenously produced plasma protein, which was in the steady state.

The data indicate that there is a marked disturbance in metabolism of the plasma proteins as well as an increase in renal permeability to them in the active stage of the nephrotic syndrome. The data thus appear to reconcile two divergent concepts concerning the pathogenesis of the hypoproteinemia which is so characteristic of this disease.

The Influence of Cortisone on the Therapeutic Efficacy of Erythromycin and Penicillin in the Treatment of Whooping Cough. Dr. George J. Ginandes, Dr. Jerome L. Kohn, Dr. Charles Chang, Dr. Sophia Chang, and Dr. Zacherias Matthews, New York.

The present study was undertaken to ascertain whether the therapeutic efficacies of erythromycin (Ilotycin, Lilly) (E) and penicillin (P) are altered by the simultaneous administration of cortisone (C). The population included 278 children with ages ranging up to 6 years, (about 70% under 2 years). All patients had positive nasopharyngeal cultures for Hemophilus pertussis. Patients for study were drawn by a system of random selection. The therapy in the individual patient was unknown to the observer. Mild cases and those with a duration of cough longer thar three weeks were excluded.

The subjects were reasonably well distributed among the four drug groups according to number, age, sex, clinical severity, and culture index. Thus, these four groups were differentiated only by therapeutic agent, as follows: (1) P alone, (2) E alone, (3) P with C, and (4) E with C.

The clinical status of each subject was evaluated three times in the course of the study: (1) after preliminary observation (two to five days, chiefly two), (2) one week later, i. e., on the last day of administration of the therapeutic agent, (3) one week after cessation of treatment. The clinical status at each stage was evaluated according to a numerical score or index (1 to 8), based chiefly on severity of the respiratory symptoms. This yielded three indices: preliminary severity index, categorized as moderate (score 3, 4, 5) or severe (6, 7, 8); test severity index; and final severity index, respectively. The degree of improvement observed after one week of therapy was measured by the difference between the first and second of these indices, and that one week following cessation of therapy by the difference between the second and third indices. These differential scores were designated as the first (or test) and the second (or final) improvement indices, respectively.

Clinically these improvement indices were arbitrarily divided into two groups; striking improvement (2, 3, 4); little or no improvement (0-1). The statistical technique rested on the calculation of the (arithmetical) mean improvement index for each sample of subjects grouped according to drug or other factors pertinent to the investigation. Statistical validity of differences between such mean indices was evaluated according to the student's *t*-test, at a 1% level of probability.

An analysis of the improvement index after one week of therapy indicated that the order of therapeutic efficacy of the four therapeutic agents was PC>FC>E>P, with only the relation of EC and E being not statistically significant. Thus the addition of cortisone improved the efficacy of the penicillin, but not of the erythromycin. These results were independent of pre-

liminary severity, as shown by analysis of the four drug groups broken down into moderate and severe categories. The relative efficacies of the four therapeutic agents were independent of age, sex, and preadmission duration of cough.

The final improvement indices (one week after cessation of treatment) were similarly analyzed. No important differences in the rates of improvement as between pairs of therapeutic groups were noted. There was no instance of retrogression or reversal of conditions following cessation of treatment.

Observations were made on a fifth group of patients treated with C alone (25 patients) and on a sixth group without any drug therapy (49 patients). The data indicated that all the agents used in this study, including C alone, gave a better therapeutic response than was found in the group without any drug therapy.

Conclusions.—1. The most effective of all the four groups studied was the combination of penicillin and cortisone. 2. The additions of cortisone to erythromycin induced no statistically significant improvement in the response to the latter.

Two Cases of Isolated Lipid Histiocytosis of the Spleen. Dr. F. W. Wiglesworth and Dr. R. L. Denton, Montreal, Canada.

This report concerns two 10-year-old boys with splenomegaly of several years' duration, without symptoms referable to the organ. No biochemical or hematological abnormality was found on investigation. The enlarged spleens were removed in both instances, and histologically they showed numerous foci of lipid-containing histiocytes. Chemical analyses of the spleens show a marked increase in the cholesterol content. One patient is alive and well 18 years and the other 15 months after splenectomy. This appears to be a hitherto undescribed lesion and is of uncertain etiology.

Results of Valvulotomy for Valvular Pulmonary Stenosis with Intact Ventricular Septum (Analysis of Sixty-Nine Patients). Dr. Don M. Hosier, Dr. John L. Pitts, and Dr. Helen B. Taussig, Baltimore.

The report is concerned with a follow-up of 69 patients who have had a pulmonary valvulotomy and have been followed for three months to four years after operation.

Complete information on all aspects of the postoperative results was not obtained on every patient, but whenever possible we have compared the preoperative and postoperative exercise tolerance, hemograms, arterial saturations, and changes in the size of the heart. Whenever possible the cardiac changes were correlated with the findings of cardiac catheterization.

Subjective improvement was noted in all but two patients. The comparison of the preoperative and postoperative auscultatory findings did not prove to be of significance in the evaluation of the operative result. The comparison of the hemograms and arterial oxygen saturations showed improvements in all but one patient.

The chief interest centered around changes in the size of the heart. Patients in whom there was no preoperative cardiac enlargement naturally showed no changes after operation. Among the patients with cardiac enlargement, the majority of adults showed an initial prompt decrease in the size of the heart after operation, whereas most of the infants showed increase in the size of the heart in the early postoperative period.

In the long-term studies in order to evaluate the factor of growth, the cardiothoracic ratio as well as the actual size of the heart was studied.

Patients who had attained full growth showed a marked decrease in the size of the heart and thereafter showed no further change. The cardiothoracic ratio decreased and then remained constant.

In children, the most favorable change was for the heart to return to normal size and thereafter for the heart and chest to grow together and the cardiothoracic ratio to remain constant.

The next most favorable finding was when the heart, although it decreased in size, remained enlarged; and then over a two- to three-year period the heart remained constant in size, the chest grew, the cardiothoracic ratio fell, and eventually the heart returned to normal size.

In a few instances, the heart was seen to decrease in size and subsequently to increase again. This is regarded as evidence of insufficient relief of the pulmonary stenosis.

In those patients who had cardiac catheterization preoperatively and postoperatively, it was found that when the right ventricular pressure dropped to less than 100 mm. of Hg cardiac enlargement came to an end.

Congenital Aortic Stenosis: Early Clinical Manifestations and the Late Development of the Classical Syndrome. Dr. Helen B. Taussig, Baltimore.

Aortic stenosis is the counterpart on the left side of the heart of pulmonary stenosis on the right side. In both the obstruction may increase as the patient grows. Either one may lead to great cardiac enlargement and cardiac failure. Obviously accurate diagnosis is the essential prerequisite for treatment.

Recent experience in the Harriet Lane Home Cardiac Clinic has shown that the clinical findings in mild subaortic and aortic stenosis may closely resemble those of a septal defect. Two of our patients were originally diagnosed as having auricular septal defects because of a systolic murmur over the pulmonic area, a tendency to a right axis deviation, and a hilar dance; another was diagnosed as a ventricular septal defect because the murmur and thrill were maximal close to the left sternal border in the third and fourth left interspaces, but cardiac catheterization showed no evidence of any shunt. In each instance it was only as the patient grew and the obstruction increased in severity that the clinical picture changed and the patient finally developed classical signs of aortic stenosis, i. e., a basal systolic murmur and thrill to the right of the sternum transmitted to the vessels of the neck, a narrow pulse pressure, and electrocardiographic evidence of left ventricular strain.

These observations indicate that the so-called "classical" findings of aortic stenosis are the late clinical manifestations of congenital aortic stenosis. Furthermore, the early signs of congenital aortic stenosis are totally different from the early signs of rheumatic aortic stenosis.

Surgical correction of aortic and subaortic stenosis is more difficult than that of pulmonary stenosis, in part because of the necessity to enter the left ventricle and in part because of great variation in the pathology. The stenosis may be valvular, or there may be a membranous subaortic shelf of tissue, or there may be a muscular ridge of tissue beneath the aortic valve. In one of our patients the aorta at its base was abnormally small. Nevertheless it is reasonable to hope that with improvement in surgical technique, the malformation, at least in some instances, will be amenable to surgery.

Until that time comes the finding of classical signs of aortic stenosis is a strong indication for restriction of activity.

Selective Angiocardiography in Infants and Children. Dr. Richard D. Rowe, Dr. Peter Vlad, and Dr. John D. Keith, Toronto, Canada.

The methods of selective angiocardiography originally described by Jonsson for older children and adults has been applied to infants and young children.

In a limited experience with 50 cases, the technique has been found particularly valuable in studying anatomical and hemodynamic details not always revealed by the classical venous technique.

Selective angiograms from patients with tetralogy of Fallot, pulmonary stenosis with normal aortic root, transposition of the great vessels, tricuspid atresia, single ventricle, isolated ventricular septal defect, auricular septal defect, and anomalous pulmonary venous drainage are reproduced.

The relative merits of venous and selective techniques in this age group are discussed briefly. It is concluded that the venous angiogram is especially helpful in very small infants with cyanotic heart disease and that the selective method is of greatest value where the broad anatomy of the defect is suspected prior to the study but where particularly clear visualization of a certain area is required.

The Clinical Syndrome of Persistent Ostium Primum. Dr. James A. Manning and Dr. Helen B. Taussig, Baltimore.

Recent surgical advances have made the closure of simple auricular septal defects, that is, defects in the septum secundum, a relatively safe procedure. In contrast, the closure of defects in the septum primum is technically far more difficult, may require a different surgical approach, and carries a much higher operative mortality. Therefore, the differentiation of defects of the ostium primum type from those in the septum secundum is of great clinical importance.

This paper discusses the embryologic differences between defects in the ostium primum and in the ostium secundum and brings together clinical and physiologic data on four patients, three of whom have come to autopsy. Analysis of these cases indicates that a persistent ostium primum presents a characteristic clinical syndrome.

Patients with this defect have, in general, more cardiac symptomatology than do those with the simple ostium secundum defect. The heart is enlarged and often shows evidence of progressive cardiac enlargement. There is a long, harsh, systolic murmur low along the left sternal border, which is also heard well at the apex with transmission to the axilla. The pulmonary second sound is accentuated. X-rays show enlargement of all four chambers of the heart and evidence of increased pulmonary vascularity. The electrocardiogram has the unusual combination of a left axis deviation in the standard leads, with evidence of either right or combined ventricular hypertrophy in the precordial leads. Cardiac catheterization has shown evidence of a large left-to-right shunt at the auricular level, no shunt between the ventricles, only moderate right ventricular hypertension, and no peripheral arterial oxygen unsaturation.

Autopsy has uniformly shown a crescenteric defect in the septum primum extending down to the base of the auricular septum at the point of fusion of the mitral and tricuspid valves. In each instance, there has been a deformity of the anterior leaflet of the mitral valve causing mitral insufficiency. All have had dilatation and hypertrophy of all four cardiac chambers and intact ventricular septa. A defect in the mitral valve appears to be of common occurrence in the ostium primum defect and may contribute to the seriousness of the malformation.

Finally, the major points of differentiation of this syndrome from the defects in the septum secundum, from the anomalies of venous return, from ventricular septal defects, and from the syndrome of persistent atrioventricularis communis are discussed.

Proteolytic Enzyme Inhibitor. Dr. Frederic C. Moll, Seattle.

Proteolysis is a common phenomena associated with inflammation due to hypersensitivity or infection and may precede the release of histamine and heparin. Studies to be reported have been made concerning the behavior of the heat-stabile, nonspecific proteolytic enzyme inhibitor occurring in serum using as the test enzymes both trypsin and the enzyme obtained from human white cells.

The experimental work done in monkeys showed that the proteolytic inhibitory activity of serum was increased when animals were stressed with sterile abscess. Apparently this response was due to tissue destruction, since it occurred with stress from salicylates and cold and did not occur with cautery necrosis or following extensive irradiation. In adrenal insufficiency associated with prolonged cortisone administration or during sudden withdrawal of cortisone, the response of the inhibitor to stress was an indolent one as to the rate and magnitude of the inhibitor response. Cortisone produced a dramatic and immediate rise in the inhibitory power of the serum. This response reached its maximum in two to four days and then fell somewhat despite subsequent administration of cortisone. These responses suggest that the rise in the serum inhibitor due to stress and cortisone represents a defense mechanism to protect against proteolysis accompanying the inflammatory response. The behavior of this inhibitor and the hyaluronidase inhibitor is quite similar in response to stress, but the proteolytic inhibitor is heat-stable, behaves differently in clinical conditions, and partial purification has been obtained from human plasma which retains the proteolytic inhibitor action but does not inhibit hyaluronidase.

The significance of these studies lies in the attempt to define the mechanism of the anti-inflammatory action of the adrenal hormones and suggests that the proteolysis associated with the inflammatory reaction is modified by the serum inhibitor which in turn is controlled by the adrenal.

Acute Benign Pericarditis: Prevalence in Splenectomized Patients with Cooley's Anemia. Dr. Carl H. Smith, Dr. Marion Erlandson, Dr. Irving Schulman, Dr. Mary Allen Engle, and Dr. Gertrude Stern, New York.

In recent years a form of acute pericarditis has been recognized which does not fall into one of the previously established categories and has been variously termed benign, nonspecific, idiopathic or primary. It is usually ascribed to a nonbacterial, viral etiology. Despite its frequency in adults, this condition has been less commonly described in children.

Over a period of four years acute benign pericarditis was diagnosed in five splenectomized patients, aged 9-19 years, with severe Mediterranean anemia. While the signs varied considerably, the symptoms and electrocardiographic changes were typical of pericardial inflammation. Of 38 children with severe Mediterranean anemia under supervision in the past 10 years, splenectomy was carried out in 24. The occurrence of 7 attacks of acute benign pericarditis in

5 splenectomized children is significant, since no cases were observed in the comparable group of 14 children with intact spleens, and since there were only two other cases in the pediatric age group during the same period. The preponderance of this condition in the splenectomized group prompted a consideration of causative factors.

Hemosiderosis with iron deposition in the pericardium and adjacent structures seems an unlikely inciting factor, since the same condition prevails in the nonsplenectomized group. This pathologic state cannot, however, be entirely discounted and may exert a contributory influence.

It is worthy of note that in all cases of severe Mediterranean anemia in children beyond the age of 4 years, regardless of splenectomy, the γ-globulin content of the serum was significantly increased and ranged from 1.39 to 3.16 gm. per 100 cc. These elevations probably represent disturbed liver function rather than hypergammaglobulinemia associated with increased susceptibility to infection. The immunological characteristics of this γ-globulin fraction in the splenectomized and nonsplenectomized patients are still unknown and await investigation.

The predilection of certain patients with severe Mediterranean anemia for infection by the agent responsible for benign pericarditis may conceivably reflect a state of increased susceptibility following splenectomy. Although available evidence with large groups of patients splenectomized for various conditions does not substantiate a causal relationship, there are circumstances that suggest more than a fortuitous association. Two patients in our splenectomized group of severe Mediterranean anemia succumbed to fulminating infection, one within two weeks following the operation, the other within a year. In another report, a similar overwhelming infection was encountered in a small group of young children following splenectomy for spherocytic anemia. In the light of these occurrences, serious consideration should be given to the prompt treatment of any illness in young patients following splenectomy. Further investigation is planned to determine the immunological response of splenectomized patients with various blood disorders.

Depot Fats and the Effect of Ethionine in Experimental Nephrotic Hyperlipemia. Dr. Walter Heymann, Cleveland.

The nephrotic syndrome was produced in rats by the intravenous injection of anti-rat-kidney-sera obtained from rabbits. In animals with established renal disease and hyperlipemia, the total carcass fat was found to be increased. The corresponding average values were 25 gm. of fat per 100 gm. of dry carcass obtained in 14 controls, as compared with 32 gm. noted in 14 nephrotic animals. This would amount to approximately 5-6 gm. more depot fats in a nephrotic rat weighing 200 gm. The amount of fat found in the liver was the same in both groups.

The possibility that the increased concentration of plasma lipids in nephrotic animals would result in increased deposition of fat in the depots had to be considered. It was found, however, that in addition to other depot fats, the liver fat increases markedly when control rats were given a high fat diet. An increased deposition of plasma lipids thus does not explain the high carcass fat values obtained in nephrotic rats.

The administration of 10-15 mg. of ethionine per 100 gm. of rat to 12 nephrotic animals reduced the excessive blood lipid concentration to subnormal values within three to five days. This occurred regularly with a simultaneous increase of liver fat, without affecting other depot fats. The course of the renal disease, the degree of proteinuria, etc., remained unaffected by the alteration of blood lipid concentration.

Conclusions.—Increased depot fats with normal amounts of lipids in the liver have been noted in nephrotic rats. This finding does not support the contention that the nephrotic hyperlipemia is due to increased mobilization of depot fats or to increased fat intake. It is consistent with a diminished rate of lipid degradation.

The Dangers of Pipette Feeding of Premature Infants with Medicinal Oils. Dr. F. M. B. Allen, Belfast, Northern Ireland.

One hundred fifty-eight infants (of whom eighty-two were premature) were investigated radiologically after the administration of contrast oils.

It has been demonstrated that the oily solutions given by pipette tend to "spill over" into the bronchial tree; this may be partly attributable to the relative inefficiency of the laryngeal reflex but partly also to the physical character of the oily suspension. Premature infants showed that

the contrast medium continued to enter the lungs up to 6 weeks of age (and even up to 12 weeks in some of the more immature infants), whereas in normal infants the bronchogram was demonstrable even up to 4 weeks.

The danger of administering vitamin supplements in an oily state to infants in the early days of life is emphasized.

Glutamic Acid Dehydrogenase and Transaminase in White Blood Cells from Patients with Leukemia. Dr. Harry A. Waisman, Carl Monder, and J. N. Williams Jr., Madison, Wis.

Glutamic acid dehydrogenase in white blood cells was studied as part of an investigation of the enzymes involved in the metabolism of amino acids in the various blood constituents. Eighty per cent of the white blood cells was isolated from the supernatant plasma of whole heparinized blood after allowing the red blood cells to settle by gravity at room temperature. Further separation of white blood cells could be obtained by inducing rouleaux formation of the red blood cells with 0.8% dextran. Red blood cells had no detectable glutamic dehydrogenase activity. Enzyme activity was liberated from the white blood cells by alternate freezing, thawing, and homogenization. The rate of reduction of added DPN was measured in a Beckman Model DU spectrophotometer in a system containing 1.1 ml. of phosphate buffer, 0.60 ml. of 0.5 N potassium glutamate, 2×10^7 white blood cells, 0.1 ml. of 1% DPN, all at pH 7.6. The values are expressed as change in optical density per cuvette per 30 minutes per 1000 white blood cells (Δ OD_{30}). The average Δ OD_{30} for 19 nonleukemic patients was 14 ± 17 and for 32 leukemic patients, 62 ± 45. There was no significant difference in the values obtained from patients with the chronic or the acute leukemias. Changes in enzyme activity of the white blood cells during the course of the disease were followed in several patients.

Glutamic-aspartic transaminase (oxalacetate-glutamate as substrate) was present in plasma, but higher values were obtained in white blood cells. Red blood cells had no activity. No apparent differences in transaminase activity were found between leukemic and nonleukemic white blood cells.

The Incidence of Milk Allergy in Pediatric Practice. Dr. C. Collins-Williams, Toronto, Canada.

In order to assess the incidence of milk allergy in private pediatric practice 3000 office patients varying in age from birth to the 15th birthday are reviewed. These patients make up the usual office population of a practicing pediatrician and are consecutive patients with the following exceptions: 1. All patients seen at any time for major allergy are excluded, since there is an undue proportion of these in the author's practice. 2. All consultation cases are excluded if it was suspected that the referring doctor sent the patient because he thought he might be allergic, since there is an undue proportion of these in the author's practice. 3. All cases that came directly to the office where the mother considered the child allergic are also excluded, since this would give an unfair rating towards allergy.

This series of cases has certain defects which will influence the incidence of milk allergy discovered. 1. Exclusion of the three groups of cases listed above lowers the reported incidence, since the practicing pediatrician has many cases of major allergy and a few cases which fall into the other two groups. This is compensated for by the fact that in these three groups of cases the pediatrician should always think of milk allergy, and the reported incidence will therefore apply to the hidden cases of milk allergy which the pediatrician must ferret out for himself. 2. The almost routine use of evaporated milk prevents an inestimable number of infants showing sensitivity symptoms to milk, since evaporated milk is less apt to cause symptoms than ordinary bottled milk. 3. Some of the patients were not seen until later childhood, and therefore it was impossible to evaluate whether they had been allergic to milk in early life. 4. Many of the infants were breast-fed and were therefore not exposed to cow's milk during the first few months of life.

In the 3000 cases there were 9 cases of definite milk allergy, giving an incidence of 0.3%. Clinical manifestations of milk allergy observed were colic, vomiting, diarrhea, severe buttocks rash, melena, celiac syndrome, severe behavior disorder, and acute anaphylactic shock.

Studies on the Etiology of a Human Respiratory Disease and Its Relationship to Canine Distemper. Dr. John M. Adams and Dr. David T. Imagawa, Los Angeles.

In addition to previously reported studies indicating the pathological and immunological relationship of primary pneumonitis in infancy and canine distemper, we are presenting evidence of a further etiological relationship based on experimental data. Material employed was obtained from human beings and consisted of throat washings, tonsils and adenoids, and urine sediment. Because distemper involves the urinary system as well as the respiratory system of dogs and ferrets, urine sediment from human beings was studied and found to contain pathological cells with characteristic cytoplasmic inclusion bodies. Following ultracentrifugation, the sediment was employed for isolation and immunologic studies in tissue culture and animals.

In our laboratories we have developed a neutralization test for the detection of specific antibodies against distemper. The test is based upon the reaction of chick embryos to inoculation of a mixture of serum and living egg-adapted distemper virus. The successful development of the neutralization test has made possible the following applications: (1) detection of neutralizing substances against distemper infections; (2) determination of the specificity of the occurrence of the antibodies; (3) the identification of the causative viral agent; (4) the study of antigenic relationship between canine distemper and respiratory and urinary tract infections of human beings.

In the first series of experiments, ferrets were given multiple inoculations with human material. Serum from the ferret was checked for its protective effect against distemper, and all of the animals including the controls were then challenged with 100 M.L.D. of virulent distemper virus. Protection was demonstrated in a significant number of animals. The animals which were protected had an increase in distemper antibody titer of at least tenfold when the serum collected before immunization was compared to serum collected after immunization. Animals including the controls which succumbed to the challenge showed no rise in titer.

In the second series, antibody responses were observed in those animals receiving human material. The controls again failed to respond. However, following a severe challenge with virulent distemper virus, all animals eventually died; but the animals with elevated antibody titers showed a significant increase in survival time. Consequently, a third series of studies is now under way to confirm and establish the specificity of the previous results.

Distemper has been successfully adadpted to mice, and neutralization studies with human serum and gamma globulin have been accomplished. In addition, tissue culture techniques are being employed for isolation. At present several strains of viruses have been successfully isolated from human beings.

Conclusions.—Further evidence of a relationship between a human respiratory disease and canine distemper has been presented. Ferrets were successfully immunized against distemper with human material consisting of pathological tissue suspensions. Studies with mouse-adapted distemper virus confirmed the previous reports that distemper virus can be neutralized by human serum and human γ-globulin.

Tissue-Culture Diagnosis of Poliomyelitis and Aseptic Meningitis. Dr. Mary O. Godenne, New Haven, Conn.

The intraduction of tissue-culture methods in the field of viral diseases has given the physician a new and helpful laboratory tool in the diagnosis of poliomyelitis infections. However, to be of practical value in clinical diagnosis, results from the laboratory have to be obtained as soon as possible after the patient's admission to the hospital. In a study carried out by the Yale virus diagnostic laboratory, these criteria have been fully evaluated. Ninety-six pediatric and adult medical patients admitted between July and December, 1954, to the Grace New Haven Community Hospital were included in the series; the cases were selected on the basis of their clinical diagnosis. There were 49 patients with paralytic poliomyelitis, 41 with aseptic meningitis or nonparalytic poliomyelitis, and 6 with a clinical picture of "encephalitis."

On admission of the patient a throat swab, rectal swab, blood sample, and in most instances a cerebrospinal fluid specimen were obtained; the earliest stool specimens collected after admission were saved for virus studies. A convalescent serum was secured two to three weeks later.

Specimens were tested immediately for the presence of virus by inoculation of monkey-kidney tissue cultures. A poliomyelitis virus was isolated from some source in 44 out of 49 paralytic

cases, in 13 out of 41 patients with aseptic meningitis, and in 3 out of 6 cases of "encephalitis." Stools were the best specimens for the isolation of poliomyelitis virus. In one instance, a Type I poliomyelitis virus was isolated from the cerebrospinal fluid of a child with paralytic poliomyelitis.

In 60% of the patients from whom a poliomyelitis virus was obtained, the agent was recognized and typed within seven days of the time of inoculation of the specimen. By two weeks after inoculation these positive results were available in 88%. Poliomyelitis complement fixation and neutralization tests were performed on acute and convalescent sera samples. The antibody titers obtained in the paralytic patients from whom a poliomyelitis virus was isolated provided the basis for the diagnostic criteria of these tests. The results of the complement fixation and neutralization tests were considered together to be of diagnostic significance in 96% of the patients from whom a poliomyelitis virus was recovered.

Conclusions.—We believe that the results obtained by the tissue-culture diagnostic laboratory have been of value to clinicians and to patients as well. It has been demonstrated that the clinical impression of nonparalytic poliomyelitis may be confirmed by laboratory studies. Of the various tests now available the isolation of poliomyelitis virus is the most valuable and results can be secured in a matter of days. Antibody studies are also indispensable, and the complement fixation test has been particularly useful, for complement fixation antibodies are a more reliable index of recent poliomyelitis infection than are neutralizing antibodies, which may only be a reminder of past infection.

Further Observations on Infantile Idiopathic Hypoglycemosis. Dr. Irvine McQuarrie, Minneapolis.

During the past five years, 18 typical cases of infantile idiopathic hypoglycemosis have been studied in our own clinic. Many other single cases have come to our attention in widely scattered communities throughout the United States and Canada. The principal features of the syndrome are as follows: (1) early age of onset (23 of 28 cases had first distinct symptoms before the age of 18 months); (2) absence of any characteristic physical stigmata; (3) symptomatology varied and easily overlooked; (4) all special tests for liver, adrenocortical, thyroid, and pituitary insufficiency negative; (5) familial tendency to spontaneous hypoglycemia strong (13 cases found in four unrelated families in our series of 28 cases); (6) natural tendency to recover or undergo marked amelioration with age; (7) uniformly favorable response to corticotropin therapy or large doses of cortisone or hydrocrotisone. Most cases cease to require hormone therapy after a few months' therapy. A few still require the hormone in minute doses over two years.

In the latter, supplementation of corticotropin by pituitary growth hormone, thyrotropic hormone, gonadotropin, and lactogenic hormone separately or together showed no intensification or inhibition of hyperglycemic effect of corticotropin.

Conclusions.—Diagnosis of infantile idiopathic hypoglycemosis is simple when it exists and is tested for. This error of carbohydrate metabolism is far more common than diabetes mellitus among infants. Corticotropin therapy appears to be as efficacious in infantile idiopathic hypoglycemosis as insulin is in diabetes mellitus.

Some Observations on Pulmonary Hemorrhage in the Newborn Period. Dr. J. N. Briggs, Winnipeg, Man., Canada.

The work of previous authors is reviewed. Fifteen cases of pulmonary hemorrhage are presented. Observations are made on labor and intrauterine distress, postpartum anoxia, and distress as factors in the production of intra-alveolar pulmonary hemorrhage. Intra-alveolar pulmonary hemorrhage is compared with the appearance of interstitial pulmonary hemorrhage.

A study of intrapulmonary vessels was made; no remarkable difference was noted in the nature of the elastic tissue in the walls of these vessels. The role of the vascular structure of the lung is discussed in its relationship to the production of intra-alveolar hemorrhage.

From a study of the 15 cases there appears to be a definite clinical syndrome of intra-alveolar hemorrhage in which the infant may suddenly become unwell and on several occasions there is a welling up of pure blood from the pulmonary tree. The factor of anoxia in any form is nearly always present in such cases. The onset of the clinical symptoms may be delayed for several days after birth.

Hyaline membrane and plugging of intra-alveolar ducts were present in more than half of the cases of intrapulmonary hemorrhage. These cases were examined along with a series of

newborn infants who died from other causes than intra-alveolar hemorrhage, and the same percentage of hyaline membrane was not present in the control series. The possibility of cardiac failure as a cause of this condition was considered and studied in relationship to organ weights.

It would seem that intra-alveolar hemorrhage is a clinical entity. There is a history of preceding respiratory distress followed often after by an internal of abnormality, by increased respiratory difficulty, a sudden terminal rush of blood from the lungs associated with marked pallor, and sudden death.

The Effect of Hypoxia on the Blood Barrier as Measured by Radioactive Iodinated Serum Albumin. Dr. Lawrence B. Slobody, Dr. Dorothy C. Yang, Dr. Miriam Lending, Dr. Frank J. Borrelli, and Marjorie Tyree, B.A., New York.

Postmortem examinations of newborn infants and animals have indicated that hypoxia is often associated with cerebral capillary dilatation, edema, transudation of plasma, and hemorrhage. Our studies have been with hypoxia in living subjects—human and animal. This report is concerned with the effect of hypoxia on the blood-brain barrier of puppies and older dogs as measured by the migration of radioactive iodinated human serum albumin (RISA) from blood to cerebrospinal fluid.

Puppies and older dogs were made hypoxic using varying mixtures of nitrogen and oxygen. Controls consisted of dogs of similar ages and weights treated with a sham procedure and some dogs who served as their own control prior to induction of hypoxia. Oxygen saturation studies were made in some instances with a Waters-Conley oximeter and by the Schowlander method.

RISA (6-10 μc/kg.) was injected intravenously; samples of cerebrospinal fluid (cisternal) and plasma were obtained simultaneously at variable intervals from the control and hypoxic dogs. Radioactivity was measured in the well type scintillation counter and recorded as counts/second/ml. Specific activity of the plasma and cisternal fluid samples was determined as counts/second/mg. total protein.

In 10 puppies, the first samples, taken two hours after the induction of hypoxia, uniformly demonstrated increased cerebrospinal fluid radioactivity (range 3.8-7.5 counts/second/ml.) as compared with the controls (range 0.6-1.6 counts/second/ml.). The ratio of specific activity between the cisternal fluid and plasma in the hypoxic puppies was also increased over that of the controls. The older dogs were apparently more resistant to this effect of hypoxia, and only some of these dogs demonstrated moderately increased cerebrospinal fluid radioactivity as compared with the older dogs acting as controls. It required several days following the induction of the hypoxia for the cerebrospinal fluid radioactivity to return to levels approximating those found in the nonhypoxic animals.

The use of a single intravenous tracer dose of radioactive iodinated human serum albumin seems to be a helpful index of the permeability of the blood-cerebrospinal fluid barrier. Following hypoxia, in puppies the early appearance of significantly increased cerebrospinal fluid radioactivity as compared with the controls suggests that hypoxia is associated with increased permeability of the blood-brain barrier in these puppies. This method is being used to evaluate agents which may aid in preserving the integrity of the blood-brain barrier.

The Effect of Cortisone in Different Types of Experimental Glomerulonephritis and Nephrosis. Dr. K. Lange, Dr. R. Strang, and E. J. Wenk, M.S., New York.

Serum-complement levels fall with the onset of the disease in nephrotoxic glomerulonephritis and nephrosis as an expression of a complement-binding antigen-antibody reaction. The fall occurs in anuric animals as well as in animals with ligated ureters.

In the nephrotoxic nephrosis of the rat produced by anti-rat-kidney rabbit serum, the fall of complement is immediate but is only very short-lived (less than 24 hours). Albuminuria occurs immediately and persists subsequently for varying lengths of time together with hypercholesteremia and sometimes uremia followed by death. This behavior of complement differs from the one found in the human disease, in which complement stays low throughout the active phase of acute and subacute glomerulonephritis and in most circumstances of the nephrotic syndrome. The rat disease produced by anti-rat-kidney rabbit serum cannot be prevented or altered by cortisone medication.

In rabbits a glomerulonephritis or a nephrotic picture can be produced by anti-rabbit-kidney duck serum. This disease will occur only five to seven days after the initial injection, even when

the initial amount of serum is large. Serum complement falls shortly prior to the onset of clinical and laboratory findings of the disease. This fall of complement occurs even when the animal is anuric. As in the human disease, complement stays low for many days or weeks. Whether a nephritic or nephrotic picture occurs is determined by the amounts of the nephrotoxic serum used. Large amounts tend to produce a nephritic picture, while small amounts produce nephrotic features.

The rabbit disease leads to a temporary elevation of B. U. N. and a slow rise of cholesterol. The albuminuria may be very heavy in the nephrotic type or moderate with red cells and casts in the nephritic type. This disease can be either completely prevented or ameliorated and delayed by cortisone given simultaneously with or up to several days after the injection of the nephrotoxic serum. The animals successfully treated with cortisone do not show a rise in B. U. N. or cholesterol and often escape albuminuria completely or show small amounts of it.

Extraordinary amounts of nephrotoxic serum lead to an immediate massive hematuria and petechial hemorrhages into mucous membranes, but without a fall in serum complement. If the animal survives this first stage, hematuria disappears within three days, and a true nephritic picture appears after five to seven days with concomitant immunologic and laboratory findings.

In the rat disease one short-lived antigen-antibody reaction with tissue destruction takes place leaving a damaged kidney. In the rabbit disease the immediate antigen-antibody union in the kidney is not complement-binding and therefore not tissue-destroying, but autoantibodies to duck serum are subsequently formed and they localize in the kidney leading to a complement-binding, tissue-destroying antigen-antibody reaction. This autoantibody formation can be suppressed or reduced by cortisone.

Electrolyte Changes in Burns: Experimental and Clinical Studies. Dr. Charles L. Fox Jr. and Sigmund E. Lasker, M.S., New York.

Investigations of extensive thermal burns in children have indicated the need for further study of the influence of factors such as depth of burn and total surface involvement on the movements of albumin, electrolytes, and fluid which might be amenable to therapy. Accordingly, burns in mice and monkeys were studied. Groups of mice were subjected to burns of 7%, 15%, 30%, 60%, and 85% of body surface area by immersion in water at 70 C for seven seconds, as standardized by Rosenthal. The total changes were measured in each animal by analyzing all the burned tissue, all the unburned tissue, and all the viscera. The burned tissue gained albumin, water, sodium, and chloride and lost potassium; maximal swelling and shift of albumin occurred in the minimal (7%) burn. With increasing area of burn, less changes occurred, and in the most extensive burn minimal changes were observed. Although the changes per unit tissue were less in the more extensive area burns, the total change was considerable; thus the over-all electrolyte and fluid changes were approximately equal in the minimal and maximal burns. As a consequence, the sodium, water, and albumin removed from viscera and the potassium acquired were approximately similar in each type of burn.

In other experiments the area of burn involvement was held constant (one hind leg), but the severity of thermal trauma was increased to 70 C for 30 seconds, 85 C for 30 seconds, 95 C for 15 seconds. (In monkeys, the clinical course of burns produced at 85 C simulated those seen in patients.) The movement of albumin labelled with I^{131} was measured together with electrolytes and water, comparison being made between the burned and the opposite, unburned hind leg. The maximal changes, including movement of albumin into the injured tissue, occurred with the minimal thermal trauma (70 C for seven seconds). As the trauma increased, fewer shifts occurred, and the maximal burn demonstrated no significant shifts of fluid, electrolyte, or albumin. The "standard" burns, involving 7% or 14% of body surface, were not fatal; the 60% burn was fatal but amenable to electrolyte therapy; the 90% burn was fatal and not amenable to therapy. Likewise, the burns of both hind legs at higher temperatures were fatal and not amenable to therapy. These observations indicate that the changes in electrolyte, fluid, and albumin are not well correlated with survival when the burn is varied in intensity, and area of involvement and suggest that other local factors may be involved.

In studies in 20 children with extensive full-thickness burns, the dominant electrolyte changes were falling plasma CO_2 with normal plasma sodium levels initially; subnormal sodium values occurred after 72 hours despite copious intake of sodium salts. Plasma potassium levels were usually normal or low; urine potassium levels became extremely low after the first or second day.

The clinical and experimental data indicate that thermal burns produce significant changes in colloids, potassium, sodium, and body water. The direction and extent of these changes differ in burns produced at high and low temperature and in burns of varying extent of body surface area. Further studies are needed to evolve a satisfactory formula for clinical usage.

Disorders of Blood Coagulation During the First Week of Life. Dr. John R. Hartmann, Dr. Doris A. Howell, and Dr. Louis K. Diamond, Boston.

Present theory divides the in vivo phenomenon of blood coagulation into three phases: (1) the generation of thromboplastin from platelets, calcium, antihemophilic factor (AHF), plasma thromboplastin component (PTC), and plasma thromboplastin antecedent (PTA); (2) the conversion of prothrombin into thrombin by thromboplastin, and (3) the formation of fibrin from fibrinogen by thrombin. Proconvertin (Factor VII, SPCA) and proaccelerin (Factor V, Ac-Flobulin) probably function as accelerating factors late in Phase 1 and early in Phase 2.

Previous evidence has indicated an abnormality in the coagulation system of newborn infants in Phase 2, as measured by the Quick "prothrombin" test. However, it is postulated that defects in Phase 1 also exist in the blood of these normal infants. The in vitro formation of thromboplastin is retarded and frequently deficient, reaching normal control levels at 9-12 months of age. Of the factors active in Phase 1, only PTC is low, ranging between 10%-15% of normal in full-term babies and 8%-12% in premature babies. At present this phenomenon is not considered clinically significant in the normal newborn baby except to confirm immaturity of the liver where PTC is probably produced. Low PTC and poor thromboplastin generation has been noted in patients with liver disease and those undergoing bishydroxycoumarin (Dicumerol) therapy.

Variable levels of proaccelerin (62%-130%), low prothrombin (25%-40%), and low proconvertin (25%-45%) were confirmed. That low levels of the latter are not a determinant in the abnormal generation of thrombplastin is demonstrated by a normal test in a 4-year-old child with isolated proconvertin deficiency (5%-8%).

Abnormal bleeding due to specific defects in the coagulation mechanism during the first week of life was investigated in 34 patients.

Defects in the Generation of Thromboplastin.—1. Fourteen patients with classic hemophilia and two with Christmas disease. Generation of thromboplastin in three was grossly abnormal with absence of AHF from cord blood and physiologically low or congenitally absent PTC. 2. Six newborn infants with congenital thrombocytopenic purpura. 3. Four infants with "hemorrhagic disease of the newborn." In vitro generation of thromboplastin in two patients was virtually absent. In addition to very low Quick "prothrombic" activity, quantitative prothrombin ranged from 1%-6% proconvertin, less than 1%, and PTC, from 1%-3%. Defective prothrombin conversion also characterizes this condition, but it is postulated that the fundamental abnormality lies in the extremely poor thromboplastin generation.

Defects in Prothrombin Conversion.—One patient with isolated congenital proconversion deficiency.

Defects in Formation of Fibrin.—1. One case of acquired afibrinogenemia with an active fibrinolysis and low proaccelerin (4%). Postmortem study failed to verify postulated amniotic fluid embolism but revealed normal tissue fibrinogen stores. 2. Two case of congenital afibrinogenemia. Their blood failed to clot, and subsequent studies indicated absence of fibrinogen from tissue reservoirs.

Multiple Defects.—1. Three babies with severe erythroblastosis fetalis. Thrombocytopenia was associated with low prothrombin (7%-14%), low proconvertin (14%-17%), low proaccelerin (4%-55%), and in one instance with additionally low fibrinogen (25 mg. per 100 cc.). An occasional infant with severe sepsis and liver damage may have similar defects.

Infants with anoxia or bleeding organic lesions were not included in this study.

Natural History of Seventy-Three Patients with Hemophilia and Related Hemorrhagic Diseases. Dr. John R. Hartman and Dr. Louis K. Diamond, Boston.

The natural history of 62 patients with classic hemophilia (antihemophilic factor [AHF] deficiency), 9 with Christmas disease (plasma thromboplastin component [PTC] deficiency), and 2 with plasma thromboplastin antecedent (PTA) deficiency is reviewed and methods of therapy outlined.

Positive family history with sex-linked recessive transmission was noted in 63% of those with classic hemophilia and 55% of those with Christmas disease. Simple dominant pattern with incomplete transmission occurred in the PTA-deficient family. Mild allelic forms of AHF deficiency (5%-12% of normal) occurred in seven.

Laboratory studies included prolonged clotting and recalcification times and abnormal prothrombin consumption and thromboplastin generation tests. By utilizing the latter and by cross protection tests, the specific deficiencies were determined and proportionately measured.

Antihemophilic factor is absent from cord blood of a patient with hemophilia. Eighteen per cent had prolonged hemorrhage from the umbilicus or following circumcision. Four cases of mild hemophilia and two of PTC deficiency had no abnormal bleeding subsequent to circumcision. Ninety-four per cent had onset of easy bruising and/or hemorrhage from small lacerations in the mouth or tongue during the first two years. The latter injuries (32%) frequently required hospitalization, sedation, and plasma infusion. Sixty-five per cent developed hemarthoses, especially of the large joints of the legs, between 1½ and 3½ years of age. Loss of decidual teeth infrequently caused prolonged bleeding, though extraction of carious permanent ones always necessitated hospital admission and plasma infusion. Nosebleeds were seldom bothersome, responding to local Oxycellthrombin application but rarely requiring plasma transfusion. Gastrointestinal hemorrhage was unusual (6%) but at times serious and difficult to control. Hematuria (10%), most frequently followed trauma, lasted 10 days or more, and responded poorly to plasma but much better to combined plasma-cortisone therapy. Hemorrhage into the soft tissues of the neck associated with infection or dental extraction (18%) and bleeding intracranially following trauma (6%) constituted the most serious complications. One death occurred from the former, two from the latter. Repeated hemarthroses occurred in 85% of the patients, with resultant joint deformity of moderate to severe degree in 30%. Early immobilization, plasma infusions, and gradual return to activity may prevent crippling residuals. Hemorrhages into deep muscular compartments have caused ischemia, palsy, and atrophy of distal parts if untreated. One patient with mild hemophilia underwent a successful appendectomy. An increased hemorrhagic tendency followed infections (45%) but could not be significantly related to seasonal variation or other causes.

Resistance to normal plasma infusions developed in three children with hemophilia and one with Christmas disease. Cortisone did not affect the blood-coagulation mechanism but appeared to help control small vessels bleeding by a vasoconstrictor effect.

Fresh blood or plasma, freshly frozen plasma, lyophilized antihemophilic plasma, or active Fraction I preparations corrected the clotting abnormality in those with classic hemophilia. One cubic centimeter per pound was given intravenously every six hours. Any of the above, except Fraction I, plus regularly stored bank plasma or dried plasma corrected the Christmas factor and PTA defects. One to 2 cc/lb. was given intravenously every 12-24 hours.

Some Pediatric Implications of the Vanderbilt Cooperative Study of Maternal and Infant Nutrition. Dr. Calvin W. Woodruff, Edwin B. Bridgeforth, A.B., Dr. Margaret P. Martin, Dr. William J. McGanity, and Dr. William J. Darby, Nashville, Tenn.

The Vanderbilt Cooperative Study of Maternal and Infant Nutrition includes appraisals of dietary intake, nutritional physical evaluations, and biochemical assessments of nutriture once each trimester and six weeks postpartum. Independent appraisals of clinical performance of mothers and infants were made. Over 2000 consecutive admissions to the prenatal clinic during 1945 to 1949 are included.

This report relates the performance of the infants to maternal nutriture. The relation of birth weight to maternal size is considered in comparisons including birth weight. No relationship to maternal caloric or protein intake was found.

The mothers of premature infants present a pattern of relative underweight, higher hemoglobin concentrations in the third trimester, lower vitamin C intakes and serum ascorbic acid levels than do the mothers of full-term infants.

Congenital malformations occurred in 2.6% of the infants. A search for associated deviations in the nutriture of their mothers was entirely negative.

The hemoglobin concentration of the infant at birth and at the age of 6 weeks showed no variations which could be related to the nutritional status of the mothers.

The nutritional level of these mothers is above that at which it becomes the determining factor in these pediatric complications. Consequently attempts to reduce the incidence of these complications should be directed toward investigating their etiology rather than supplementing the diets of the mothers.

A Controlled Study of the Development of Premature Infants: I. Status at Forty Weeks of Age. Dr. Hilda Knobloch, Rowland V. Rider, ScD., Dr. Benjamin Pasamanick, and Dr. Paul Harper, Baltimore.

As part of a long-term study of premature infants, 499 premature infants and 491 matched full-term control infants born in Baltimore in 1952 were examined when they were approximately 40 weeks of age. The purpose was to determine whether differences in growth and development exist between those infants weighing 2500 gm. or less at birth and those weighing over 2500 gm. The aspects studied included physical growth, the incidence of serious illness, congenital defects, cerebral palsy, mental deficiency, convulsive disorders, gross visual and auditory defects, and minimal cerebral damage.

The premature group comprises all single-born infants who weighed 1500 gm. or less at birth and a sample of those weighing between 1501 and 2500 gm. Full-term controls were matched by the following characteristics: race, plurality, season of birth, parity of mother, place of birth, and census tract of residence.

Information was obtained by means of special reports while the infant was in hospital and again on discharge concerning prenatal care, complications of pregnancy, labor, and delivery, and the infant's course in hospital. This was supplemented by subsequent review of hospital records and by a history obtained at the time of 40-week examination which checked some of the above observations and added interval information.

Examinations were scheduled as close to 40 weeks of age as possible, and almost all were done by one physician. They consisted of a physical examination and a Gesell Developmental Examination. The infants were divided into three diagnostic categories: those infants who were considered normal, an intermediate group who showed departure from normal behavior but appeared to require no particular follow-up, and an abnormal group which showed sufficient deviation from expected 40-week behavior to warrant careful observation to determine the prognosis for future development.

Preliminary analysis of the data indicated that as the birth weight increases an increasing percentage of infants are called normal. Differences between the birth-weight groups are statistically significant. When the cases are adjusted for differences in birth-weight distribution there is no difference in the proportion of abnormal cases between whites and nonwhites. There is no evidence that the incidence of mental deficiency differs between premature infants and full-term controls, but the incidence of serious neurological defect and of minimal cerebral damage is significantly greater in the premature group. Approximately 40% of the infants in the weight group 1001 to 1500 gm. have a major handicap at 40 weeks of age.

Sulfonamide Administration in Newborn and Premature Infants. Dr. Elaine G. Fichter and Dr. John A. Curtis, New Orleans.

As part of a long-term program to compare the sulfonamide drugs and various other antibacterial agents in newborn and premature infants, a basic study was undertaken to establish the optimum dosage and interval of administration of sulfonamide drugs in such infants. Specific studies of this nature have not been previously reported.

Fifty healthy infants were studied. Of these, 25 were full-term newborn infants, 13 were premature newborn infants, and 12 were premature infants between the ages of 1 and 6 weeks.

Following the administration of parenteral 5% sodium sulfadiazine and oral triple-sulfonamide suspension, serial blood sulfonamide levels were determined on capillary blood samples. Free and total sulfonamide levels were determined in most instances.

All newborn infants, both term and premature, who received on the first day of life a single subcutaneous injection of sulfadiazine, 100 mg/kg. body weight, maintained a satisfactory blood sulfonamide level for 48 hours. The average 6- and 48-hour levels were 14.4 and 9 mg. per 100 cc. in the full-term infants and 11.7 and 6.6 mg. per 100 cc. in the premature infants. Levels ranging from 6.6 to 17.4 mg. per 100 cc. were subsequently maintained by single 24-hour doses of 50 mg/kg. body weight subcutaneously or (full-term newborns only) by single 12-hour oral doses of 50 mg/kg. body weight.

The older premature infants maintained significant blood levels for only 12 hours following a single dose of 100 mg/kg. body weight, either subcutaneous sulfadiazine or oral triple-sulfonamide suspension. For this reason it was necessary to administer the subsequent doses, both subcutaneously and oral, at 12-hour intervals to achieve levels ranging from 4.6 to 18.7 mg. per 100 cc. This dosage schedule is comparable to that generally accepted for older infants and children.

No complications of therapy and no crystalluria or hematuria were observed in any of these infants.

The importance of the oliguria of the early newborn period in maintainance of blood levels is evident by contrasting the newborn premature infants who maintained a 48-hour level following a single dose of sulfadiazine with the group of premature infants between 1 and 6 weeks of age who maintained a significant level for only 12 hours following the initial dose.

The full-term newborn infants maintained blood levels somewhat higher than the premature newborn infants on the same subcutaneous dosage schedule. Since the elimination of sulfonamide depends primarily upon renal excretion, which is more closely related to surface area than to weight, the most likely explanation for the lower levels in the premature infants is their relatively greater surface area.

It was interesting to note the very limited amount of acetylation that occurred in all of the infants where both free and total sulfonamide levels were determined. This suggests some hepatic immaturity or insufficiency in regard to the function of acetylation. Since the acetyl derivatives are therapeutically less active, this limitation of acetylation in infants should increase the efficacy of sulfonamide therapy.

It is apparent from our data that in the newly born infant satisfactory intervals of administration of sulfonamide drugs are 48 hours following the initial dose and 24 hours for subsequent doses. While the sulfonamide levels obtained with such a schedule average well above the accepted therapeutic range, it does not follow that more frequent administration of the drug and much higher blood levels would necessarily be harmful.

Nonbacterial Pharyngitis in a Group of Cleveland Families. ELI GOLD and HAROLD S. GINSBERG, Cleveland.

During July and August of 1954 there occurred in Cleveland an epidemic of nonbacterial pharyngitis attacking particularly children and characterized by fever and sore throat. From cases in a group of 65 families under medical observation by the Department of Preventive Medicine, throat washings and blood specimens were obtained. Agents cytopathogenic for HeLa cells were isolated and found to be antigenically identical to the Type II and III adenoid degeneration (A. D.) agents of Rowe, Huebner, and co-workers. Neutralization tests in HeLa-cell tissue cultures revealed that in 28% of the 65 families one or more individuals showed a rise in titer of neutralizing antibody to the Type III A. D. agent during the summer of 1954. Seventeen per cent of the children and 43% of the adults had detectable antibody in the spring of 1954; none of these showed a further rise in antibody titer during the summer epidemic. Of individuals exposed to this illness by its presence in a member of the family, 64% of the children and 10% of the adults who did not possess type-specific antibody at the time of exposure were infected by the Type III A. D. virus, as proved by development of neutralizing antibodies.

Complete medical records and multiple specimens of sera accumulated during the six years of the family study were reviewed in an attempt to elucidate the importance of the Type III A. D. virus as an etiologic agent in previous respiratory infections. Although illnesses clinically identical to those seen during the summer of 1954 were frequently recorded, only a few of these illnesses were associated with the Type III A. D. agents.

Summary.—The etiology and epidemiology of a summer epidemic of nonbacterial exudative pharyngitis has been reviewed. The agent described appears to have caused similar epidemics in the past, but it is not the sole cause of this syndrome.

Treatment with Intramuscular Iron. DR. WILFRID GAISFORD, Manchester, England.

In the treatment of iron-deficiency anemias in infants, iron by mouth, both in the ferric and ferrous forms, is uncertain in action in many cases, causes digestive upsets in others, and has to be continued for some time before the hemoglobin reaches and stays at a satisfactory level. The technical difficulties inherent in intravenous iron therapy in babies and small children are

well known. For these reasons a potent intramuscular preparation of iron causing no untoward local or systemic effects would be of great value. Such a preparation has been used for the past year in two groups of patients. Firstly, a series of infants with iron-deficiency (nutritional) anemia. The results were so uniformly good that a second group—of premature infants—was treated, and in this group a trial was made, both of prophylactic therapy in the newborn period in the hope of preventing the development of the otherwise inevitable anemia at 4 to 6 months of age and as therapy for established anemia of prematurity. A control series was observed concurrently in the trial group.

The preparation used contained 50 mg. of iron per ml., and the dose necessary to raise the hemoglobin to normal was calculated from the formula Fe in mg.=1.31×(17—Hg. [in G])×wt. (in lb.).

The injections—0.5 or 1.0 ml. in volume—were generally given on alternate days, but they can be given twice daily if necessary.

Treatment as an outpatient has been found perfectly satisfactory.

Some 50 children have been treated in the first group and 33 premature infants in the second, together with 20 controls. Marrow punctures and siderocyte counts were undertaken in many of the cases both in older infants and in the premature group at the start of the trial.

In the first group the total iron necessary has been of the order of 250-350 mg., entailing less than a week of treatment with an injection once daily.

In the premature infants the dose was either 150 or 250 mg.

The Nephritic Sequelae of Henoch-Schoenlein's Purpura. Dr. R. J. Wedgwood and Dr. M. H. Klaus, Cleveland.

Seventeen boys and nine girls were examined 1 to 15 years after the acute phase of an attack of Henoch-Schoenlein's purpura. At the time of onset of purpura their ages ranged from 1 to 12 years; 13 had a history of a preceding or concomitant respiratory infection, and 5 of 9 cultured harboured beta-hemolytic streptococci. The acute phase lasted between 6 and 180 days, usually subsiding in 4 weeks. During the actue phase nine had hematuria and/or proteinuria; four of these also had hypertension.

By history all had been well in the 1- to 15-year follow-up interval. At follow-up, in addition to a pertinent interval history and physical examination, an Addis count was made on a 12-hour urine collection. When abnormal, the Addis count was repeated, often several times, and if the abnormality persisted, further studies were performed.

Ten of the twenty-six had consistently abnormal urine, characterized by hematuria and cylinduria rather than proteinuria, on follow-up. The length of follow-up and the sex ratio of this abnormal group was similar to the group with normal urine. However, the ages at onset differed; 9 of 13 over the age of 6 years at onset had abnormal urine on follow-up, in contrast to only 1 of 13 under the age of 6 years. A similar age difference was found relating to the presence of normal or abnormal urine during the acute phase of the disease. However, urinary abnormality during the acute phase was not invariably associated with abnormal urine on follow-up, nor was normal urine during the acute phase necessarily associated with normality following the disease. Four of the ten with abnormal urine had maximal urea clearances below 70% of normal, and one failed to concentrate his urine during water deprivation.

Considering the character of this urinary abnormality in relation to the known renal lesion of this disease, Henoch-Schoenlein's purpura should again be considered as a not infrequent cause of possible latent nephritis in older children and adults.

Studies of the Occurrence and Significance of a Heparin-Precipitable Protein in Human Plasma. Dr. Richard T. Smith, Minneapolis, and Dr. Lewis Thomas, New York.

Previous studies in this laboratory have indicated that the fibrinoid material which is deposited in the lumen and walls of small blood vessels during the development of the generalized Shwartzman reaction is derived in part from fibrinogen. It was observed in the course of experiments attempting to define the nature of the coagulation defect in the Shwartzman reaction that a qualitative alteration of circulating fibrinogen is regularly produced in rabbits by a single intravenous injection of Gram-negative bacterial endotoxin. This alteration is manifested by cold-precipitation of fibrinogen by heparin. The present report is concerned

with the identification, characterization, and measurement of a similar heparin-precipitable fraction in the plasma of children and adults and with the changes in the amount of this material which occur during various diseases.

A method of quantitative estimation of the fraction based upon its insolubility at 4 C has been developed. Results of studies to date indicate that small amounts of the heparin-precipitable fraction, in the range 0.03 to 0.15 gm. per 100 cc., are found in normal plasma. Newborn infants have very low values—0.005 to 0.03 gm. per 100 cc. Marked increases in this fraction, with levels as high as 1.4 gm. per 100 cc., were encountered in the plasma of children with acute rheumatic fever, rheumatoid arthritis, acute glomerulonephritis, Hodgkin's disease, and acute bacterial infections. Serial measurements have shown that the high initial values returned to normal paralleling the clinical response to therapy. In children with acute rheumatic fever, for example, prompt decreases were observed following steroid or salicylate therapy.

Evidence that this fraction is identical with or closely related to fibrinogen may be summarized as follows:

1. Absence from serum.
2. 30%-50% clottability by thrombin.
3. Migration as a single peak, parallel to fibrinogen, on paper electrophoresis.

In normal plasma the heparin-precipitable fraction was 25%-50% of the total fibrinogen value, while in acutely ill patients the levels often equalled or exceeded total fibrinogen. Further studies of the physicochemical characteristics of the fraction are in progress.

Data gathered to date are consistent with the conclusion that heparin-precipitable fraction of human plasma represents a qualitative alteration of circulating fibrinogen, reflecting the presence of inflammatory or necrotizing disease, and that the magnitude of this change is roughly proportional to the severity of the process. Implications of the occurrence in certain diseases of increased precipitability of fibrinogen in combination with high molecular weight acidic polysacchardes will be discussed.

Comparative Studies of Proteinuria and Hematuria in the Nephrotic Syndrome and Glomerulonephritis. DR WALTER HEYMANN. Cleveland.

Albumin and globulin determinations were carried out by electrophoresis (Tiselius method) on the urine of 32 nephrotic and 12 children with acute glomerulonephritis. The results of 95 determinations obtained over a two-and-one-half-year period will be reviewed with reference to possible prognostic implications. The nephrotic children were divided in two groups: (*a*) those who at no time had hematuria, azotemia, or hypertension; and (*b*) those patients who did show persistent symptoms of progressive renal failure. A statistically significant difference was noted in that nephrotic children whose disease progressed to renal failure usually excreted more globulin. In 5 out of 7 of these patients the globulin excreted in the urine in 24 hours varied between 2 and 3.25 gm., whereas none of the 25 nephrotic children whose disease took a favorable course excreted more than 2.0 gm. per day at any time. The albumin-globulin ratio in the urine of the former was close to 1.0, in the latter, 2.25.

In acute glomerulonephritis the albumin-globulin ratio was 1.25. The duration of proteinuria is, however, usually much shorter, and the amounts of protein excreted are considerably smaller.

The gross hematuria noted in 5 nephrotic and 12 patients with acute glomerulonephritis revealed distinct differences. A bright red color was noted in seven of nine nephrotic urines. Of the RBC, 70%-96% showed a well-preserved morphology. The sedimentation rate in the urine was slow, and the supernatant was free of hemoglobin. Among the 17 nephritic urines, 13 were of dark, brownish color, well-preserved RBC between only 10% and 56%; their sedimentation rate was rapid, and in 12 instances the supernatant was of brownish tinge.

Conclusions.—The albumin-globulin ratio in the urine of nephrotic children whose disease took a favorable course was 2.25, and the amounts of globulin excreted per day did not exceed 2.0 gm. If the disease progressed to renal failure, the ratio was close to 1.0 and the globulin excreted in 24 hours varied between 2.0 and 3.25 gm. This may at times be of practical value in the prognostic evaluation of nephrotic patients.

Gross hematuria in nephrotic patients gives rise to a bright red color of the urine and the RBC are well preserved. In acute nephritis the hematuric urine has a dark brownish tinge and the RBC have been hemolized to a large extent.

Transposition of the Great Vessels: A Clinical Evaluation. Dr. Melville I. Singer, Dr. Edward C. Matthews, and Dr. Samuel Kaplan, Cincinnati.

Transposition of the great vessels has been found to be the commonest cause of death in infants with cyanotic congenital heart disease at the Children's Hospital, Cincinnati. The purpose of this report is to describe the clinical and pathologic features of this condition as observed in a large series of patients in order to aid in the diagnosis of the malformation and to evaluate the effects of surgery. Fifty cases are presented in whom the diagnosis of transposition of the great vessels was proved.

The clinical history is reviewed with respect to sex, birth weight, growth and development, age of onset of symptoms, presenting symptoms, family history, abnormalities of the pregnancy, and history of respiratory infections. The average age of death in the group was seven months.

Physical examination was characterized by cyanosis, congestive heart failure, and cardiomegaly. The significance of the presence or absence of heart murmurs will be discussed.

Electrocardiographic studies were made in 42 cases. In nine instances only the three standard leads were included. The remaining 33 electrocardiograms included the standard leads as well as unipolar extremity and chest leads. P pulmonale and right ventricular hypertrophy were the characteristic findings. The significance of left ventricular dominance in infants with transposition of the great vessels will be discussed.

Roentgen studies were made in 47 cases. These will be reviewed with reference to heart size and configuration, presence of the characteristic narrow base on posteroanterior view with widening in the oblique position, ventricular and atrial enlargement, and pulmonary vascularity.

Postmortem examinations were performed in 44 cases. The result will be presented with special attention to heart size, evidence of chamber hypertrophy, origin of the coronary arteries, pathologic changes in the lungs, associated anomalies, and cause of death where ascertainable. Special attention will be given to associated cardiovascular anomalies such as patency of the foramen ovale, atrial and ventricular septal defects, patent ductus arteriosus, coarctation of the aorta, and valvular stenosis and atresia. The presence of these associated defects will be correlated with the clinical course in an effort to ascertain the combination of abnormalities which permit survival.

Review of the literature has shown that patients with transposition of the great vessels who survive to adult life have had the associated defects of pulmonary stenosis and large intracardiac shunts. Six patients were subjected to surgery in an attempt to create these associated abnormalities. The results of successful surgical therapy in two instances will be presented.

Insulin and Growth. Dr. Douglas Hubble, Derby, England.

Best and his co-workers have shown that a slow-acting insulin will maintain growth in hypophysectomized rats.

All the features of the Mauriac syndrome in diabetic children (five patients)—dwarfism, florid facies, hepatomegaly, obesity, hypercholesterolemia, and sexual infantilism—can be explained by the known effects of the corticosteroids. The pathogenesis of the syndrome depends on a deficiency of insulin, particularly during the night, which allows an enhanced activity of the corticosteroids. In one patient who died the large liver was filled with glycogen; in two patients treatment by long-acting insulin was shown by nitrogen balances to increase the retention of nitrogen, and this experimental observation has been confirmed by better-than-average growth in the succeeding two years. The regression of other features, such as hepatomegaly, can be explained by the recession of adrenocortical activity.

Hypopituitarism occurring in diabetic adolescents (two patients) is characterized by dwarfism and sexual infantilism and can be explained by defective anabolism of protein (insufficient insulin) or by increased breakdown of protein (gluconeogenesis by corticosteroid action). Hypopituitarism was overcome in both patients by the use of long-acting insulin with adequate control of the diabetes through the 24 hours.

In three dwarfs, two with presumed hypopituitarism and one of the Lorain type, no increased growth could be demonstrated by prolonged insulin therapy, although increased nitrogen retention had been demonstrated in nitrogen balances. In the two hypopituitary dwarfs, who had normal adrenocortical function, there was weight gain with increased fat deposition. This is presumably the difference between these patients and Best's hypophysectomized rats: insulin does not fully overcome the protein-katalreic action of the corticosteroids.

Conclusions.—Insulin will promote growth in diabetic children with the Mauriac syndrome and in uncontrolled diabetic adolescents with hypopituitarism. In these latter patients the improved growth and developing sexual function may depend on improved protein anabolism associated with adequate insulin therapy; in the former group, growth depends on the depression of excessive adrenocortical activity. In dwarfs with normal adrenocortical activity insulin therapy does not promote growth.

Physiological Adaptation to Hypoxia of Congenital Heart Disease. Dr. George S. Husson, Syracuse, and Dr. Arthur B. Otis, Baltimore.

There are few recorded measurements of oxygen consumption and ventilation of individuals who are chronically hypoxic due to the presence of right-to-left circulatory shunts. Such measurements as have been made suffer from a lack of suitable control studies made under similar conditions on nonhypoxic subjects.

It was our objective to study resting oxygen consumption and ventilation in a group of 42 patients who were chronically hypoxic as a result of congenital malformations of the heart with right-to-left intracardiac shunts. Arterial saturation in this group ranged from 61% to 93%, with an average of 83%. For comparison, measurements were made under similar conditions on 45 patients with noncyanotic congenital heart disease whose saturation was 94% or higher. Patients of various ages are represented in both groups.

Methods.—Measurements were made in connection with the procedure of diagnostic cardiac catheterization. All patients were in a fasting state and were moderately sedated with morphine, scopolomine, and pentobarbital (Nembutal). Resting oxygen consumption and ventilation were measured usually after the catheterization procedure by a three-minute collection of expired air in a 100 Liter recording Tissot spirometer following two or three preliminary washout periods during which the patient became accustomed to the apparatus. The expired gas was analyzed on a Scholander 0.5 cc. analyzer for CO_2 and O_2 so that O_2 consumption, CO_2 production, and the respiratory exchange ratio could be calculated. A modification of the Nahas method was used for determining the arterial saturation of bloods drawn during the final three-minute air collection. Body surface area was estimated according to the method of Dubois.

Results.—We observed no significant difference in oxygen consumption between the group of patients with chronic hypoxia due to intracardiac anomalies and the group with anomalies but without hypoxia. We also found that the oxygen consumption in the younger age groups in both series compared quite favorably with a series of normal males. Oxygen consumption of the adult patients in the hypoxic and the nonhypoxic groups deviated significantly from the normal. It is felt that these older patients were not relaxed during the procedure.

The data on resting pulmonary ventilation on the other hand demonstrate that the chronically hypoxic congenital cardiac hyperventilates more than the nonhypoxic congenital cardiac patient. The difference between the two series in this regard is highly significant ($P < 0.01$). In addition our data show a tendency for the degree of hyperventilation to be related to the degree of hypoxia.

Conclusions.—Resting oxygen requirements in the chronically hypoxic subjects is neither depressed nor elevated, indicating no alteration in fundamental cellular metabolic processes.

Resting hyperventilation aids the cyanotic patient not in increasing arterial oxygenation, but rather in elimination of CO_2. Thus an attempt at maintenance of normal PCO_2, pH, and alkaline reserve is made by the chronically hypoxic cardiac patient.

Influence of the Parathyroid on Bone Lesions Associated with Renal Insufficiency in the Rat. Dr. William H. Bergstrom, Dr. Eugene R. Jacobs, Dr. David B. Jones, and Dr. John T. Prior, Syracuse, N. Y.

Chronic renal insufficiency may be accompanied by bone lesions involving decalcification and epiphyseal disorganization, variously termed "renal rickets" and "renal osteitis fibrosa cystica." The role of the parathyroids in the production of the bone lesions has been extensively discussed, since secondary hyperparathyroidism is a consistent finding. Previous studies have shown that the changes in question can be produced by bilateral nephrectomy in young rats as well as by the administration of parathormone in large doses to normal or nephrectomized rats. One group of investigators has reported that no change occurs if simultaneous nephrectomy and parathyroidectomy are done, implying that the presence of the parathyroid is essential to bone destruc-

tion. Since no chronic studies and no chemical data indicating the degree of decalcification were found in the literature, the following experiments were designed.

Renal insufficiency was produced in rats by unilateral nephrectomy and wrapping the remaining kidney in gauze in situ to prevent hypertrophy. The procedure was done when the rats weighed approximately 60 gm., half of the rats so treated having simultaneous parathyroidectomies. After nine weeks the survivors of both groups were killed and their bones compared with those of coeval controls. Histological examination was supplemented by analysis for ash content, calcium, carbonate, and sodium. A second series of rats, weighing approximately 100 gm., was totally nephrectomized, with simultaneous parathyroidectomy in half the animals. After 36 hours bones were compared with those of 100 gm. controls.

Survivors of the chronic experiment showed bone lesions histologically, the changes being similar but less marked in the parathyroidectomized animals. Both groups showed slow growth and elevated serum phosphorus. In the acute experiment demineralization occurred in all operated rats but was again less marked in the parathyroidectomized group.

Apparently the bone lesions accompanying acute or chronic renal insufficiency in rats are not entirely the result of parathyroid action, since they occur in parathyroidectomized animals. The fact that the lesions are more pronounced when the parathyroids are present suggests that they have at least a dual origin.

Prematurity-Jaundice-Kernicterus Syndrome. Dr. V. Mary Crosse and Dr. Thomas C Meyer, Birmingham, England.

Sixty cases of kernicterus (not associated with hemolytic disease) have occurred among 2608 premature infants admitted to three Birmingham Units during 1951-1954.

The incidence of kernicterus decreased as birth weight and maturity increased.

Compared with all premature infants (2608) admitted and with all premature infants (5243) born in Birmingham during this period, there was (1) an excess of males and of second-born twins, (2) no significant difference between the birth order of kernicterus babies and babies in the other two series, (3) a lower incidence of toxemia and a higher incidence of nontoxic separation of placenta among the cases of kernicterus.

Compared with all prematures admitted, a greater number of cases of kernicterus were associated with abnormal labor, but when compared with controls (babies of similar birth weights) this was not so.

Compared with controls, the cases of kernicterus had suffered more (before the onset of kernicterus) from jaundice, edema, atelectasis, cyanotic attacks, hemorrhages from the intestine, and hypothermia on admission.

The cases of kernicterus and their controls had comparable early starvation periods, and both groups had comparable doses of vitamins B and C. Eleven of the cases of kernicterus had received more vitamin K than the controls (nine for hemorrhagic diathesis and two for ? intracranial injury). More of the cases of kernicterus had required sedation and the administration of oxygen before the onset of kernicterus.

Signs of kernicterus included jaundice, head retraction, oculogyric crises, expressionless face, anorexia (in bottle-fed babies), cyanotic attacks, alterations in muscle tone. Signs were often mild and transient and could easily have been missed in the absence of well-trained nursing staff. In 56 of the cases, the first signs appeared between the fourth and eighth days of life, with the maximum incidence on the sixth day; the onset became later as the birth weight increased.

Forty-four of the sixty cases of kernicterus died during the neonatal period; the earlier the onset, the higher was the mortality (due to the earlier onset among the smaller babies). Those who died showed typical yellow staining of the basal ganglia.

Survivors generally appeared normal for a few months, though some were irritable and had spells of stiffening and eye-rolling, but they retained their infantile reflexes for too long a period and were late with their milestones. Muscle tone was variable. Some degree of deafness and mental retardation was often found. Some of their teeth showed enamel hypoplasia. In some cases, abnormal signs only become obvious by the age of one year or more, and some of the babies who had shown only mild transient neonatal signs eventually developed into severe cases of cerebral palsy.

Hemolytic disease was excluded in all cases. Recent investigations in the units show that there is a strong possibility of the development of kernicterus when the serum bilirubin level rises

above 18 mg. per 100 cc. A higher incidence of cases of kernicterus has coincided with an increased routine dosage of vitamin K. Cases have developed with minimal dosage, and also in the absence of the administration of this drug, but vitamin K may be an aggravating factor.

Conclusions.—Dosage with vitamin K should be minimal, regular estimations of serum bilirubin should be made, and replacement transfusion should be considered if the level rises above 18 mg. per 100 cc.

Bilirubin Encephalopathy: Studies Related to Cellular Respiration. Dr. William J. Waters and Dr. Willet R. Bowen, Syracuse, N. Y.

Previous studies have identified the pigment in the brain cells of cases of hemolytic disease of the newborn as bilirubin. In addition, newborn rats have been injected with a solution of commercial bilirubin, and as a result jaundice with staining of the brain has been produced.

The comparative effect of a solution of 40 mg. per 100 cc. of bilirubin on the oxygen uptake of adult and 24-hour rat-brain tissue was measured in vitro.

Adult albino rats weighing 230 gm. and 24-hour-old albino rats weighing 3 gm. were used. The animals were killed and the brain tissue immediately chilled in phosphate buffer. A homogenate was immediately made of the adult rat brain, and pooled homogenate was made of the 24-hour rat brain. The flasks and solutions were kept chilled. The contents of each flask were as follows:

The Control Flasks	The Bilirubin Flasks
1.4 cc. of 1-5 dilution of brain phosphate buffer homogenate	1.4 cc. of 1-5 dilution of brain phosphate buffer solution
0.2 cc. KOH	0.2 cc. KOH
0.2 cc. of 10 mg/cc. of glucose solution	0.2 cc. of 10 mg/cc. of glucose solution
0.4 cc. of phosphate buffer	0.2 cc. of 4 mg/cc. of bilirubin solution
	0.2 cc. of phosphate buffer

PO_4 = 0.04 M — KH_2PO_4 at Ph 7.6

Bilirubin solution = 40 mg. of Hoffmann-La Roche commercial bilirubin; 0.3 cc. of 0.75 normal NaOH and 9.3 cc. of the above PO_4 buffer.

Data expressed in oxygen uptake in cu. mm. O_2/mg/hr.:

Adults
6 runs on six different days:
6 control flasks 0.40 ± 0.01 — Hence, inhibition 22 ± 1%
6 bilirubin flasks 0.31 ± 0.01

24-hour
5 runs on five different days:
5 control flasks 0.30 ± 0.02 — Hence, inhibition 67 ± 2%
5 bilirubin flasks 0.10 ± 0.01

Conclusions.—A 40 mg. per 100 cc. bilirubin solution produces inhibition of oxygen consumption in vitro in both adult and newborn brain homogenates. The striking reduction, however, is revealed by the newborn homogenates with a 67% inhibition, whereas adult brain reveals only a 22% inhibition.

Absent Pulsations in All Extremities. Dr. Arnold L. Johnson, Dr. Scott Dunbar, Dr. David R. Murphy, and Dr. Robert H. Lennox, Montreal, Canada.

A pulseless state in all four extremities is a rare but striking clinical finding in a patient who is apparently well. In cases of coarctation of the aorta, with characteristic absent or diminished femoral pulsations, a similar reduction may be observed rarely in the pulsations of the vessels in either the right or left arm, indicating an anomalous origin of the right or left subclavian artery distal to the site of coarctation.

The present discussion is centered about the anomalies demonstrated in a 5-year-old boy in apparent good health in whom the striking findings were the absence of pulsations in the arms and legs in the presence of good pulsations in the carotid arteries. A diagnosis of coarctation of the aorta with both subclavian arteries arising distal to the coarcted segment was established on the basis of these clinical findings, and this arrangement was subsequently visualized by retrograde aortography. Simultaneous intra-arterial pressure recordings in the left carotid and right brachial arteries established the pressure relationship above and below the site of coarctation.

This is an extremely rare combination of aortic arch anomalies, and we have been able to find only one previously reported case. This is striking inasmuch as it is an anomalous arrangement which may be diagnosed by clinical signs. The embryological considerations are reviewed.

The Participation of Bone Sodium in Total Body Sodium Metabolism in the Acidotic Rat. Dr. William H. Bergstrom, Syracuse, N. Y.

Approximately 30% of total body sodium is found in the mineral portion of the skeleton. Previous studies have indicated that bone sodium content decreases in acidosis, the decrement presumably being available to the total sodium economy. The present experiments were planned to investigate the following points: 1. What proportion of total body sodium loss in acute acidosis is borne by bone sodium? 2. During recovery from acidosis, what proportion of the sodium retained is sequestered in the skeleton? 3. Is bone sodium affected by changes in body fluid pH without large losses of sodium?

Adult rats were depleted of sodium and made acidotic by four hours of transperitoneal dialysis against ammonium chloride. Forty-eight hours after the procedure bones, serum, and total carcasses were analyzed for sodium, calcium, chloride, and water. Other groups so analyzed included rats subjected to the same depletion procedure but treated after 48 hours by injecting sodium-containing solutions or by allowing a normal dietary intake for several days. Rats were also made acidotic by continuous administration of acetazoleamide (Diamox) for 13 to 16 days prior to analysis. The effect of dialysis superimposed on the above regimen was also noted.

Total bone sodium content was corrected for extracellular sodium by the use of bone chloride content and Donnan-corrected serum sodium and chloride concentrations. Values for intracellular sodium in normal and acidotic rats were calculated from the data of Cotlove and his associates for animals subjected to an identical depletion procedure.

Analysis 48 hours after dialysis indicated an average sodium loss of 21% of original total body content. Fifty-two per cent of the loss was sustained by extracellular fluid, twenty-eight per cent by bone sodium, and twenty per cent by intracellular sodium. Bone sodium remained low following parenteral or oral repair, although significant total sodium retention was proved by analysis in the former instance and inferred from recovery of body weight in the latter. Acetazoleamide treatment was followed by a total sodium loss of 6 mEq. per kilogram and a bone-sodium decrement equal to that following dialysis. Additional dialysis after acetazoleamide treatment effected no further decrease in bone sodium.

It is concluded that bone sodium contributes a substantial proportion of total sodium loss in acute acidosis, that under the conditions studied no skeletal sequestration of sodium occurs during repair of acidosis, that changes in the pH of extracellular fluid are probably essential to the mobilization of bone sodium, and that the fraction accessible is limited.

The Nature and Action of Adrenal Corticoids in the Newborn: Preliminary Report. Dr. R. Klein, J. Fortunato, M.S., C. Byers, B.S., and Dr. P. Taylor, Pittsburgh.

We have been interested in the relationship between adrenal function in the newborn period and that in patients with congenital adrenal hyperplasia. We are also trying to prove the occurrence or nonoccurrence of a sodium-excreting hormone and to ascertain the validity of Eagle's hypothesis that the increased "blue chromogens" excreted by the newborn are the result of increased secretion of corticosterone (Compound B).

The corticoids in the blood of newborn infants and older children and adults have been examined after corticotropin (ACTH) stimulation. In addition, corticoids have been eaxmined in the urine of these different groups before and after corticotropin stimulation. The Bush technique of paper chromatography has been used to give preliminary identification and to separate the compounds. Final identification has been accomplished by use of the Zaffaroni sulfuric acid chromogen technique. There are limitations to this method.

The following substances which have been isolated as individual steroids from different adult urines by various workers have been found in the urine of normal children aged 3 to 10 years: tetrahydro F, tetrahydro E, tetrahydro A, tetrahydro B, and either allotetrahydro B or tetrahydro S. In addition, on one occasion 11-α F was also found. This has not previously been reported.

In the urine of newborn infants, tetrahydro F and tetrahydro E were found, as well as Compound F itself. Tetrahydro B was also demonstrated in small amounts and in addition there was a substance that ran on paper chromatogram with Compound A and gave Zaffaroni peaks of 475, 385, and 280, which would suggest that it is a stereoisomer of Compound F.

The urine from one patient with congenital adrenal hyperplasia, a 2-week-old infant, was also studied but was entirely different in its behavior on paper chromatography and on Zaffaroni acid chromogen examination. The question of the validity of this one examination arises. No definitive statement can be made about it at the present time.

Compound F was identified in the serum of older children and adults. When pooled sera obtained from newborn infants after corticotropin injection is chromatographed by the Bush technique there are two and sometimes three different corticoids demonstrated on Blue Tetrazolium staining. One of these occupies the position of Compound F and is presumably this material. The other two have not yet been identified by the Zaffaroni technique. Neither material runs at the rate of Compound B.

So far there is nothing to identify adrenal function in the newborn with that in cases of congenital adrenal hyperplasia. The fact that the newborn has other than Compound F freely circulating in its blood may be a result of poorer conjugation and degradation mechanisms rather than a change in secretion. Whether any of these different hormones are responsible for sodium loss in the newborn or in the patient with adrenal hyperplasia is, of course, unknown. These findings do not mean that there is no corticosterone in the blood of newborn infants but merely that the level after corticotropin is below what can be measured by these techniques (i. e., roughly 10 γ per 100 cc.).

Rickets with Alkaline Phosphatase Deficiency. Dr. Bernard Schlesinger, Dr. Joseph Luder, and Dr. Martin Bodian, London, England.

From a study of three cases a clear-cut syndrome is described comprising severe skeletal dysplasia associated with a low serum alkaline phosphatase. Hypercalcemia is commonly present with a posiitve calcium and phosphorous balance. Impairment of renal function may also occur. Vomiting, anorexia, and failure to gain weight are the main features, and sometimes fever, symptoms no doubt of the hypercalcemia. Rickets is often suspected at first, but the early age of onset, tense bulging fontanelle, atypical radiological changes, peculiar histological pattern, and, above all, the low alkaline phosphatase cannot be reconciled with this diagnosis. A hereditary factor seems to be present in some cases.

The x-ray features are characteristic and are generalized throughout the skeleton. Metaphyses, epiphyses, and periosteal regions are all involved. The skull in particular shows defective ossification, but later there is premature closure of the sutures and thus craniostenosis may ultimately cause blindness through increased intracranial pressure.

Biochemical estimations reveal a reduction in phosphatase activity in excised portions of bone and periosteum, while histological examination indicates an abnormal organic matrix and quantitative and qualitative deficiency of osteoblasts.

The disorder can be expected to take a favorable course eventually, although the serum alkaline phosphatase remains low and there appears to be no guarantee that the kidneys will fully recover from any damage that may have occurred. A fatal prognosis is usually associated with extremely low levels of serum alkaline phosphatase, hypercalcemia with resultant severe renal damage, and an advanced state of the disorder early in infancy.

It is suggested that the primary fault may be osteoblastic formation and that it would not be unreasonable to call this condition osteoblastic dysostosis.

The abnormal excretion of ethanolamine-phosphoric acid in the urine, detected by chromatography, is mentioned and its significance discussed.

Effect of Corticotropin (ACTH) and Cortisone Therapy on A-V Conduction of Children. Dr. John H. Githens, Dr. Matthew L. Gibson, and Dr. John A. Lichty, Denver.

In the U. K.-U. S. Cooperative Study of ACTH, Cortisone and Salicylate therapy for Rheumatic Fever, serial observations were made of the P-R intervals. These revealed a shortening of the A-V conduction time in a larger percentage of each hormone-treated group than of the acetylsalicylic-acid-treated group during the six-week course of therapy. The

possibility was considered that corticotropin and cortisone exerted some direct effect on A-V conduction which might be independent of any antirheumatic effect. Preliminary results of two approaches to testing this hypothesis are presented.

First Approach.—The normal P-R interval for each of 276 rheumatic children in the Cooperative Study was estimated on the basis of values obtained at both six months and one year from the end of drug therapy. Only those cases showing close agreement (within 0.02 seconds) between the six-month and one-year values were included. This estimated normal was used as a baseline for determining changes in A-V conduction. During the period of maximum hormone effect, from 14%-19% of the steroid-treated patients showed a shortening of P-R interval of 0.03 seconds or more below the respective baseline values.

These patients were separated into two subgroups (Table). The subgroup with P-R of 0.16 seconds or greater showed a reduction of at least 0.03 seconds below the estimated normal in 29%-36% of the cases. The subgroup with P-R of 0.15 seconds or less showed this effect in only 8%-11% of cases.

Similar changes were noted in the acetylsalicylic-acid-treated cases, but the corresponding frequencies were only 8% in the total group and 11% and 6% in the subgroups.

These changes became less evident in all treatment groups as dosage was gradually reduced.

Second Approach.—The effect of oral cortisone on A-V conduction was studied in a group of 18 nonrheumatic children. Cortisone acetate (Cortone, Sharpe & Dohme, Division of Merck & Co., Inc.) was given for a six-week period in conjunction with supplemental potassium and

Per Cent of Cases with P-R Reduction at Time of Maximum Therapy at Least 0.03 Seconds Below Their Estimated Normal

Drug	Per Cent	Subgroup with Long P-R, Per Cent	Subgroup with Short P-R, Per Cent
Corticotropin	19	36	11
Cortisone	14	29	8
Acetylsalicylic acid	8	11	6

restriction of sodium. At the time of maximum therapy a reduction of 0.02-0.03 seconds was observed in the P-R interval of all those children who had baseline P-R's of 0.16 seconds or greater. A similar but less marked change was noted in some of the children with an initial P-R of 0.15 seconds or less.

An increase in heart rate was not associated with decrease in A-V conduction.

The evidence from both studies suggests that steroid therapy in the regimens employed may produce a direct effect (reduction) on the A-V conduction time of children, irrespective of any effect on rheumatic disease. This was found to be more evident in children whose normal P-R intervals were 0.16 seconds or greater.

Observations on Forty Babies of Diabetic Mothers 1948-1954. Dr. Harry Medovy and Dr. Gerald H. Holman, Winnipeg, Man., Canada.

This is a review of 40 infants of diabetic mothers delivered at the Maternity Pavilion, Winnipeg General Hospital, 1948-1954. It includes all such infants delivered in the hospital during this period. There were four neonatal deaths, all associated with hyaline-membrane formation. In addition, 13 infants who survived had respiratory distress of varying degree. Thus a total of 17 out of 40 infants manifested respiratory distress. This fits in with the experience of others who have pointed out that the respiratory tract of an infant of a diabetic mother is peculiarly vulnerable to hyaline-membrane formation. Investigation of this relationship is important as a possible means of solving the mystery of this condition. Convulsions occurred in two infants in the nursery period. These were associated with normal blood sugars but low serum calcium. Tremors and excessive irritability were observed in a few infants, but it was not possible to relate these signs definitely to the presence of low blood sugar. Serial electrolyte study on three infants failed to disclose any significant deviation from normal. We have so far not been able to confirm the presence of an Addisonian crisis in any infant of a diabetic mother, as suggested by Gauchat.

Term delivery (14 cases, no neonatal deaths) is desirable wherever possible, and the dogmatic acceptance of "routine" delivery at 36 weeks' gestation and of "routine" Caesarean section is to

be deplored. The added risk of hyaline-membrane formation in the latter groups must be considered before these procedures are attempted. There was no correlation between the duration of diabetes in the mother and the outcome of pregnancy. The occurrence of previous fetal death, even when repeated, did not apparently prevent some mothers from finally producing a normal living infant. The analogy to similar pregnancy histories among mothers with rhesus incompatibility is noted.

Avenues for futher investigation are suggested. The riddle of hyaline-membrane disease may possibly be solved by a study of the factors which are responsible for its greater frequency among babies of diabetic mothers.

Dynamics of Hypocaloric Dwarfism. Dr. John D. Crawford and Dr. Nathan B. Talbot, Boston.

This paper will present data showing that in otherwise healthy preadolescent children deceleration in the rate of statural growth is seen not only when body weight falls from normal to subnormal levels but also when the obese child reduces fat stores and approaches normal weight. This influence of caloric turnover on linear growth is manifest throughout the years of active statural increase prior to the adolescent growth spurt. The latter characteristically occurs at the expense of body fat stores.

Despite the wide attention given by nutritionists and statisticians to the relation between caloric intake and statural growth, children with hypocaloric dwarfism continue to comprise the great majority of the patient group with short stature referred for diagnosis to the Adolescent Endocrine Clinic of the Massachusetts General Hospital. So subtle is the natural adaptive response in growth to caloric malnutrition that except in cases of extreme food deprivation simple clinical inspection of these patients may not suggest the correct diagnosis. The model weight age-height ratio in such patients has a value of 0.91. It has become apparent that hypocaloric dwarfism should be given primary consideration in the differential diagnosis of any preadolescent child presenting with short stature and in whom weight age is less than height age and bone age lies intermediate between the height and chronologic ages. Certification of the diagnosis depends upon demonstration of significant acceleration in linear growth rate when weight age is advanced to equal or exceed height age for a three-to six-month period. With successful therapy the linear growth rate may reach 15 cm. per year or more. Where treatment is not given or is unsuccessful, the relative statural deficit in childhood cannot be expected to be overcome either by an adolescent growth spurt of greater than normal proportions or through prolongation of the growth period as a function of delayed maturation.

Three categories of hypocaloric dwarfism are encountered. Rarely seen at present in this Clinic population is the child who has been denied access to adequate food. Slightly commoner is the child whose caloric intake has been insufficient primarily as the result of a simple mechanical problem, such as harelip or cleft palate. In these first two categories therapy presents little difficulty. By far the largest group consists of those children who refuse to eat a calorically adequate diet. Here great difficulty may be encountered in effecting successful therapy. Frequently, dramatic results in overcoming anorexia and resultant dwarfism have been obtained in foster home environments, but separation of the child from his family carries a high risk of aggravating basic emotional problems. Therapeutic success may be undone when the child is returned to his natural home. Experiences with a variety of approaches to this problem will be discussed.

Tolerance of Infants and Children to Fat Administered Intravenously with Particular Reference to Induced Ketonemia. Dr. Margaret Lyman Williams and Dr. Robert Kaye, Philadelphia.

The preparations (Lipomul, Upjohn) used in this study consist of 15% of olive and cotton-seed oil in 4.2% glucose solution, stabilized by soybean phosphatides and Pluronic F-68, and provide 1518 Cal. per liter.

One hundred twenty-one infusions of approximately six hours' duration have been administered to 60 subjects between 13 days and 12 years of age, with 55% of the experimental group under 1 year. The infusions provided approximately 50 Cal/kg. and were administered at an average rate of 5 cc/kg/hr. (range, 1.5-9 cc.).

Febrile reactions were encountered in 26% of infusions, with elevations generally of the order of 2 F and of short duration. These reactions were in part related to infusion rate as shown by

reduced incidence (13.6%) in 66 infusions administered at rates below 5 cc/kg/hr. Four older children developed urticaria, in one instance associated with dyspnea and cyanosis, which cleared completely in 30 minutes.

Thirteen infants under 21 months and two children of 6 years received courses of four to six daily infusions, with all of the subjects exhibiting weight gains. Oral feedings were well tolerated during infusions. Blood chemical examinations were carried out before and after the course of infusions, with no change noted in serum nonprotein nitrogen, alkaline phosphatase, bilirubin, and cephalin-cholesterol flocculation. There was a single instance of moderate elevation of zinc turbidity. Routine urinalysis and urine urobilinogen values were likewise unchanged. In four infants there was a moderate drop in hemoglobin and red blood cell count, and in five infants a definite reticulocytosis was noted.

In 34 subjects changes in blood ketones at the end of six-hour fat infusions were determined. In subjects infused under nonfasting conditions blood ketones rose to an average value of 10.5 mg. per 100 cc., expressed as acetone, while fasted subjects showed an average postinfusion level of 18.6 mg. per 100 cc. The data indicate some utilization of fat during the period of infusion and provide evidence that the accumulation of blood ketones is not of sufficient magnitude as to disturb the acid-base balance.

The rate of clearing of the infused fat was investigated in 16 experiments by serial determinations of blood turbidity during and following the infusions. In more than half of the cases turbidity had fallen to control levels at three hours postinfusion and in all except three instances at six hours.

The data suggest that with careful attention to rate of administration, calorically significant amounts of fat can be administered to infants without serious toxic effects. It appears at the present time that older children are less tolerant to the preparation used by the authors than are infants.

The Mechanism and Significance of Proteinuria in Nephritis and Nephrosis. Dr. Wallace W. McCrory, Dr. Charlotte Liu, and Dr. Milton Rapoport, Philadelphia.

Two factors influencing proteinuria in renal disease can be measured, serum protein concentration and glomerular filtration rate (G.F.R.). The role of abnormal glomerular permeability to protein and tubular reabsorption can only be examined indirectly. If increased glomerular permeability to serum protein is responsible for proteinuria in renal disease, molecular size of the protein particles could be expected to influence their respective rate of filtration through the glomerulus and as a result rate of excretion in urine. We have studied the amount and kind of protein excreted in 7 children with acute nephritis and 22 with the nephrotic syndrome. The determination of the renal clearance rates for albumin and the major serum globulin fractions in these subjects has been utilized to observe whether a relationship appears to exist between molecular size of protein and rate of renal excretion in renal disease. The albumin clearance was found to be higher than any of the globulin clearance rates. The mean value of the α-1-globulin clearance approached the albumin clearance (60%), while the other globulin fractions (α-2, β, and γ) had a much lower clearance than albumin (average 5%-15% of albumin clearance). The relationship was quite constant in all subjects with proteinuria of 1 gm/24 hr/square meters of surface area or more. It was not altered in the presence of gross hematuria or in relationship to variations in degree of proteinuria (1.0 to 14.0 gm/24 hr.). The results support the concept of increased selective glomerular permeability being a major factor in proteinuria. The major alteration in patients with terminal renal insufficiency was the markedly reduced G.F.R. Similar studies were obtained on seven children during the initial attack of acute nephritis. Proteinuria was distinctly less in these subjects than in nephrotics. The comparison of globulin and albumin clearance ratios revealed that they resembled the pattern of nephrotics when significant proteinuria occurred even in the presence of hematuria. These studies provide a means of assessing degree of renal damage in terms of filtration rate and permeability to albumin per unit of filtering surface. The major difference between proteinuria in subjects with nephritis as contrasted with nephrosis appears to be quantitative rather than qualitative. The ability of the adrenal steroids to induce diuresis and remission of the nephrotic syndrome is now well recognized. Using these data we can quantitate the extent of renal damage in subjects before steroid treatment. Nineteen patients were divided into two groups on the basis of the effect of cortisone on proteinuria; subjects showing complete disappearance of proteinuria during cortisone administration and those patients failing to show such response.

The data reveal that the patients becoming protein-free had less evidence before treatment of renal damage (as judged by G.F.R. and relative degree of increased glomerular permeability) than patients failing to do so. These data suggest that the patient's response to cortisone reflects the degree of renal damage.

The *d*-Xylose Tolerance Test: A Measure of Intestinal Absorption in Normal and Dystrophic Infants. Dr. Martin G. Wolfish, Dr. G. J. Hildick-Smith, Dr. J. H. Ebbs, Dr. Mary Louise Connell, and Dr. A. Sass-Kortsak, Toronto, Canada.

It has been shown that in adult malabsorption syndromes, the xylose tolerance test is a useful measure of absorption and has certain advantages over the customery glucose tolerance test. In the present study, the value of this test was explored in infants.

d-Xylose was given in a dose of 0.5 gm/lb. of body weight (1.1 gm/kg.), with a maximum dose of 25 gm., as a 10% aqueous solution, in the fasting state. Blood levels of xylose were obtained at 0, 1, 2, and 5 hours after the test dose.

A group of 55 normal infants was studied to obtain the range of normal tolerance. The results obtained in this group were fairly consistent. The blood xylose levels rose to at least 30 mg. per 100 cc. within two hours; all except four rose over 35 mg. per 100 cc.

These results were compared to those obtained in 40 infants suffering from dystrophy and suspected to have malabsorption. These included cases of celiac disease, fibrocystic disease, milk allergy, dystrophy following various infections, dystrophy due to insufficient nutrition, and dystrophy of unknown etiology.

Glucose and vitamin A tolerance tests were also performed on this group of dystrophic infants, either immediately preceding or following the xylose tolerance test. The results obtained by these three tests of absorption were compared. In a smaller group of patients the tolerance tests were repeated during the course of their illnesses, and changes in their tolerances were noted.

The xylose test was "flat" in celiac disease and in other conditions where malabsorption may be a factor. This test was consistently normal in conditions such as fibrocystic disease and dystrophy due to insufficient nutrition where malabsorption of monosaccharides is not part of the disturbance.

The results of glucose tolerance tests were much less uniform in these groups.

It would appear that the xylose tolerance test is a useful tool in the study of malabsorption syndromes in infancy.

Liver Function Studies in Regurgitation Jaundice in Infancy. Dr. A. Sass-Kortsak, Dr. D. H. Bowden, Dr. R. J. K. Brown, Dr. N. T. Jaco, and Dr. J. G. Frid, Toronto, Canada.

The differentiation between the numerous etiological factors leading to the development of a "regurgitation" type of jaundice in early infancy poses great difficulties. An attempt was made to asses the value of serial liver-function tests in this respect. Results of the investigation of 30 cases will be presented.

The patients were divided into the following groups: (1) congenital anomalies of the bile ducts; (2) jaundice following hemolytic disease; (3) "infantile hepatitis"; (4) jaundice following severe infections; (5) jaundice due to galactosemia.

Investigation of these patients included studies of bile pigment in urine, feces, and duodenal juice, serum bilirubin (direct and indirect reacting), alkaline phosphatase and cholesterol levels. Serum proteins and their fractions were measured by salt-precipitation techniques and a semi-quantitative method of paper electrophoresis. Cephalin-cholesterol, zinc sulphate, and thymol flocculation, as well as thymol and phenol turbidity tests, have been performed on the sera. A limited number of observations will be presented on serum cholinesterase and free and esterified serum cholesterol levels.

Complete or near complete biliary obstruction could be demonstrated in cases of congenital bile duct atresia, jaundice following hemolytic disease, and "infantile hepatitis." Complete obstruction did not occur in galactosemia or jaundice following infection. Serial serum bilirubin studies were a help in the differentiation of bilary atresia from "infantile hepatitis." Flocculation tests were usually negative, except in cases of galactosemia, where the cephalin-cholesterol flocculation test was uniformly positive. Serial determination of serum albumin and γ-globulin levels proved to be useful differential tests in some cases.

In addition to the above findings, liver function and detailed serum lipid studies will be presented on a case of acholangic biliary cirrhosis (MacMahon) in infancy.

Congenital Goiter in the Newborn. Dr. Alfred M. Bongiovanni, Dr. Walter R. Eberlein, Dr. William B. Anderson, and Dr. William Nagel, Philadelphia.

Three cases of congenital goiter of the newborn have been admitted to the Children's Hospital of Philadelphia during the past two years. All infants were suffering from various degrees of respiratory distress and ranged in age from 4 hours to 19 days. All had visible enlargement of the thyroid dating from birth. All were females.

The youngest infant was admitted at 4 hours of age with cyanosis, respiratory distress and anterior swelling of the neck. X-ray revealed compression of the trachea which appeared to be primarily anterior, and there was a questionable substernal mass visible as well. The protein-bound iodine on admission was "too high to read," on the 14th day of life 17.5 γ per 100 ml. of plasma, and on the 28th day 14.8γ. The child was treated medically, and within one week the thyroid gland diminished in size. The mother of this infant was said to have had hyperthyroidism, and she was treated with 5 grains (300 mg.) of potassium iodide daily from the second to the ninth months of pregnancy. The infant was discharged from the hospital in good condition on the 16th day.

The second infant was admitted at 12 hours age in critical condition, with cyanosis, crowing, and marked retraction. Following bronchoscopic examination it was decided to perform a thyroidectomy, which was accomplished at 15 hours of age. The respiratory embarrassment was thereby relieved, and there was a transient period of hypocalcemia and hyperphosphatemia which eventually subsided. Within one month there were signs of hypothryoidism, and the protein-bound iodine which had been 6.3 on the third day of life had fallen to 1.6. This infant has required continuous treatment with desiccated thyroid. The mother had an uneventful pregnancy and had taken no goitrogenic drugs or foods.

The third infant was born of a mother who had proved thyrotoxicosis during her pregnancy. She was treated with propylthiouracil, 300 mg. daily during the fifth to seventh months of pregnancy, and with strong iodine solution U. S. P., from the fifth month to the termination. In addition she received large doses of diethylstilbestrol and digitalis. At birth the infant was said to have been normal, although the mother was aware of a mass in the neck from the first day of life. The infant was admitted on the 16th day of life because of "choking spells" associated with feeding. A collar-like mass was seen in the neck extending laterally where each lobe measured 4-5 cm. in diameter. X-ray examination revealed compression of the trachea by a retropharyngeal mass of soft tissue. The pulse on admission was 250; there was severe diarrhea with weight loss, and there were signs of heart failure. The serum cholesterol was 85 mg. per 100 cc., and the protein-bound iodine during the third week of life was 18.7. The infant was treated with iodides, propylthiouracil, and oxygen for several days. There was gradual improvement, and the mass diminished in size. The patient was discharged in good condition on the 32d day of life.

The etiology of congenital goiter in two of the cases may be related to the administration of iodides or goitrogens to the mother and remains undetermined in the third. Tracheotomy may be necessary in such cases.

The Detection of Mucoviscidosis by the Determination of Saliva Chloride. Dr. Kathleen McGrady and Dr. Samuel P. Bessman, Baltimore.

A relatively simple procedure for the measurement of the chloride content of saliva has been applied to the analysis of specimens from 100 children with various diseases and 5 children with mucoviscidosis. The patients with muscoviscidosis had all been diagnosed after repeated examinations of the duodenal secretions.

A 50 ml. beaker or weighing bottle containing a pledget of cotton was weighed to the third decimal place. The cotton was then placed in the mouth of the patient or he was permitted to chew it. When it was thoroughly mostened the cotton was replaced in the container and a second weighing made. The difference between the initial and final weighings is the amount of saliva, and this is equal to the volume within reasonable limits.

The saliva was extracted from the cotton with distilled water, by decantation with pressing, and complete extraction of chloride is obtained with three one-volume aliquots of water.

The washings, contained in a 50 ml. Erlenmeyer flask, were titrated with standard mercuric nitrate using s-diphenyl carbazide as indicator (method of Schales and Schales). Two drops of nitric acid were added at the beginning of each titration.

In some cases patients expectorated into tarred beakers for a comparison of methods of collection.

It was found that the chloride concentration of saliva varied markedly with the method of collection and that consistent results were obtained only with the parotid secretion. This was obtained by placing the pledget of cotton in the patient's cheek and holding it there till it was saturated—a period of five minutes or less.

One hundred patients with various diseases had a range of 6.8-22 mEq. per liter of chloride in the parotid secretion. Five patients with mucoviscidosis had values of 27.2-58.1 mEq. per liter.

A number of factors which relate to the secretion of salivary chloride and the relation of this test to the clinical course of mucoviscidosis will be discussed.

Electroencephalographic Changes in Children During Artificially Induced Hyperthermia. Dr. J. M. Garfunkel and Dr. H. W. Baird III, Philadelphia.

Many of the convulsions which occur in the latter part of infancy and in early childhood merely represent an initial manifestation of an acute febrile illness. However, some studies have indicated that a significant percentage of children who have these so-called febrile convulsions subsequently have spontaneous seizures. Since approximately six to eight per cent of all children have febrile convulsions, it would appear desirable to be able to predict the probability of subsequent seizures in young children whose initial seizure (or seizures) occurred in relation to an acute febrile disorder. Electroencephalographic studies have, therefore, been carried out on children before, during, and after artificially induced hyperthermia. The results have been analyzed to determine whether there were differences in the tracings of children with histories of febrile convulsions from those of healthy children without such histories.

Electroencephalographic tracings were recorded in 12 children following the intravenous administration of typhoid vaccine. With two exceptions the subjects ranged in age from 3 to 6 years. In seven children there were histories of three or more convulsions associated with fever. Four children had no history of convulsions of any kind, although the twin of one had a history of febrile convulsions; in the other three children no family history of convulsions could be elicited. One child had a history of a single abnormal electroencephalogram two years prior to the induced hyperthermia. Temperatures of 102-105 F were attained in all children within one to three hours after the administration of typhoid vaccine.

The recent electroencephalograms of all children were interpreted as normal before the injection of vaccine. These became definitely abnormal in all patients, the most marked changes usually occurring during the rise in temperature. The changes consisted of high-voltage slow waves, spike and wave formations, and an increase in delta activity. Three convulsions were observed, two in the group with a history of febrile convulsions and one in the child whose electroencephalogram was reported as abnormal two years prior to the induction of hyperthermia. All electroencephalograms returned to normal within 3 days and usually within 24 hours.

On the basis of this series it is suggested that electroencephalographic changes characteristic of the convulsive state occur in children during fever. These changes are the same whether or not there is a previous history of convulsions. Caution is indicated in interpreting abnormal electroencephalograms as being indicative of disease of the central nervous system when these abnormalities are associated with a recent febrile illness.

Protein Metabolism in Nephrosis: Studies on Proteinuria. Dr. Robert Slater, Dr. Norman Kretchmer, Helen McNamara, M. A. and Dr. Henry L. Barnett, New York.

In the course of studies on means by which components of the plasma are transferred into the urine in health and disease, it became apparent that the identification and physicochemical characterization of each component was important, e.g., that the size, shape, and polar charges of the plasma constituents, ranging from the simplicity of water to the complexity of the conjugated proteins, such as lipoproteins (molecular weight = 1,000,000) must play an integral role in the dynamics of transfer across the glomerular membrane and in the competitive and preferential handling of each molecular type presented to the tubular cells.

It was anticipated that an interrelationship might exist between the rates of excretion of plasma amino acids and of plasma proteins of different molecular characteristics and that alterations in the relative rates of excretion of these several components might provide evidence concerning their handling by the kidney.

An exceptional opportunity to test this possibility was afforded during the care of a child with nephrosis, in whom it was possible to make frequent serial observations during alternate periods of relapse and of both spontaneous and induced (cortisone) remissions.

Contrary to the reports of others, no evidence of hyper-amino-aciduria was observed at any time in this child or in nine other children excreting variable quantities of protein. However, marked changes were observed in the ratios of the clearances and rates of excretion of different plasma proteins determined by immunochemical analysis, which provides the only reliable microquantitative method for identifying, within a mixture, individual proteins having different molecular structures.

Observations made at the time of maximum proteinuria and just prior to the disappearance of proteinuria revealed the following: the ratios of both the clearances and the rates of excretion of albumin (molecular weight = 62,000) to γ-globulin (molecular weight = 160,000) decreased from 19 to 7. Variation in the rate of excretion of albumen appeared to be the principle factor influencing these ratios.

Similar studies carried out during variable rates of protein excretion in four children with orthostatic proteinuria did not follow the above pattern. The urinary albumin/γ-globulin ratios of 4 to 7 remained relatively constant during variations up to one-hundred-fold in the excretion rate of protein.

The lack of correspondence between the patterns of protein excretion in children with nephrosis and with orthostatic proteinuria does not preclude a role of tubular reabsorption of protein. However, the observations are more readily explained as a function of glomerular permeability.

Use of Anabolic Steroids to Reduce Hypercalcemia and Hypercalcuria Caused by Immobilization in Paralytic Poliomyelitis. Dr. Donald Gribetz, Dr. Avon Y. Sweet, Dr. Amy M. Becker, Dr. Marvin F. Levitt and Dr. Horace L. Hodes, New York.

That hypercalcemia and hypercalcuria occur during prolonged immobilization has been well documented. This alteration in calcium metabolism is presumed to be the consequence of decreased osteoblastic activity resulting from the absence of stresses and strains to which bone is normally subject. The resultant diminished protein matrix (osteoid) precludes the normal deposition of calcium and phosphorous. Since bone resorption continues unabated, osteoporosis accompanied by hypercalcemia and hypercalcuria ensue. Previous investigators have studied the effects of anabolic steroids upon protein matrix formation in patients with various forms of osteoporosis. In an attempt to ameliorate the above sequence of adverse events with its potential fatal complications, i.e., urinary lithiasis, salt-losing nephropathy, and uremia, in paralytic poliomyelitis, anabolic steroids have been administered to five extensively paralyzed patients.

Three males and two females, varying in age from 13 to 42 years and having been immobilized for periods ranging from 4 to 18 months were studied metabolically. Two of the males were given a constant calculated calcium and protein intake, and their urines were collected for three six-day control periods and analyzed for calcium, phosphorus, nitrogen, and creatinine. Thereafter, methyl testosterone in doses of 40 and 80 mg. per day orally was administered for five to seven six-day metabolic periods. Similar studies were performed on the third male and, in addition, complete balance studies with analyses of diet and feces were done. The two female patients were given cyclic estrogen therapy of 2.5 mg. daily, and studies were made of plasma chemistries only.

During the control periods, the male patients demonstrated increased daily urinary excretion of calcium, phosphorus, and nitrogen varying from 40-680 mg., 700-950 mg., 7.5-11.5 gm., respectively. Under the influence of testosterone therapy, a reduction of approximately 40% in the urinary excretion of these elements was produced. Cocomitant lowering of the plasma concentrations of calcium occurred in these patients as well as in the two females.

These data suggest that protein-retaining agents may be of aid in restoring protein matrix and promoting the deposition of salts within the skeleton in patients immobilized because of paralytic poliomyelitis. It is hoped that the complications of hypercalcemia and hypercalcuria in these patients will be diminished by this means.

Standard regimens of these agents are being formulated for use in paralytic poliomyelitis patients.

Detection of Specific Antibody in Sera of Individuals Convalescent from Varicella and Herpes Zoster. Dr. Thomas H. Weller and Helen M. Witton, M.S., Boston.

Nine strains of virus isolated from varicella vesicle fluid and four strains of virus from the cutaneous lesions of herpes zoster have been propagated serially for varying periods of time in roller-tube cultures of human and monkey tissues. Observations on the in vitro, cytopathogenicity of these agents for various tissues have been carried out; both epithelial and fibroblastic cells are affected.

Employing virus propagated in vitro, three techniques have been successfully utilized for the demonstration of specific antibody. First, antigen in infected cells is demonstrable by the Coons fluorescent antibody method. Second, through modification of classical neutralization procedures by incorporation of antibody as a constant constituent of the nutrient medium, specific inhibition of cytopathic activity is obtained. Finally, a complement-fixing antigen may be prepared from the fluid phase of infected cultures by use of a concentration procedure. Of the three methods, the complement-fixation test appears to be the most suitable for adaptation to the problems of routine diagnosis and has been most extensively explored. In varicella, complement-fixing antibody usually is detectable four to five days after the first vesicles appear and rapidly increases in amount; eight-to sixteenfold rises in titer are commonly observed.

Of interest has been the failure by immunologic means to demonstrate significant antigenic differences between agents derived from cases of varicella and those from individuals with herpes zoster. Also the similarity of the cytopathic changes produced in vitro by viruses from the two clinical entities has been noteworthy.

The "Flush Technique" as an Aid in the Diagnosis of Coarctation of the Aorta in Infancy. Dr. David Goldring, Dr. M. Remsen Behrer, Dr. Ernest E. McCoy and Dr. Wilbur A. Thomas, St. Louis.

Coarctation of the aorta in infancy is seen with enough frequency in an active pediatric hospital service that a report of our experiences with such infants is warranted. Sixteen cases of coarctation of the aorta in infants have been admitted and studied at the St. Louis Children's Hospital since 1950. All patients in this series died, and the diagnosis was verified by autopsy.

The use of the "flush technique" for blood-pressure determinations in infants is described as it is applied to babies suspected of having coarctation of the aorta. A short colored movie to demonstrate the technique will be shown. Blood-pressure studies in the extremities of these infants are reported, and it is shown that the diagnosis may be made correctly in most instances antemortem.

The clinical picture is reviewed, and other available diagnostic procedures are described. The gross and microscopic pathological findings are reviewed, and finally the medical and surgical therapeutic approach is discussed in infants with coarctation of the aorta.

All 16 patients had a widely patent ductus arteriosus, and 9 of the patients had also an interventricular septal defect. In 5 of the 16 patients an attempt at surgical correction was made, but the infants died; medical management in the other 11 patients was also unsuccessful and ended in death.

More work is in progress in an effort to understand the hemodynamics in this congenital defect so that a successful therapeutic approach can be achieved.

Observations on the Interference of Fasting in Oxidative Metabolism. Dr. Ruth T. Gross, San Francisco.

Energy derived from the metabolism of food is released largely through the oxidative processes of the Krebs cycle. Increase in the blood levels of certain of the constituents of the Krebs cycle has been noted by other investigators in patients with metabolic derangements. In vitro studies have shown that specific poisons can lead to a "block" in the Krebs cycle, demonstrable by the accumulation of citric acid in tissue homogenates.

The measurement of arteriovenous differences of glucose in vivo has lead to a clearer picture of glucose assimilation. This technique has not been generally applied to the study of intermediary metabolism in humans. It offers an opportunity to make dynamic observations of the components of the Krebs cycle, both in the presence and in the absence of glucose assimilation.

In the studies to be presented the arteriovenous differences of citric acid have been measured in normal infants and children and in patients with metabolic disease. The findings have been correlated with simultaneous arteriovenous differences of glucose. Observations have been made after fasting and after feeding.

Observations in which the citric acid in the venous blood exceeds that in the arterial have been construed to indicate an accumulation of citric acid and possibly an in vivo "block" in the Krebs cycle.

In 14 children, ranging in age from 8 days to 3½ years, citric acid has been shown to accumulate in the venous blood after a six- to eight-hour fast. In 12 newborn infants under one week of age, the accumulation occurred in less than four hours and occasionally even with feeding. In normal individuals older than one week of age, the feeding of glucose promptly reversed the phenomenon so that the arterial level of citric acid exceeded the venous.

Patients with diabetes were studied with feedings of glucose, glucose and insulin, fructose and fructose and insulin. None of these substances completely reversed the "block" produced by fasting, glucose being the least and fructose and insulin the most effective.

In patients subjected to fasting sufficiently prolonged to produce ketosis, glucose was ineffectual in reversing the "block." These studies indicate that when glucose is not being assimilated, either in the fasting state or in patients with diabetes, there is an accumulation of citric acid, which may represent a temporary "block" in the Krebs cycle. The administration of glucose appears to reverse this phenomenon promptly in individuals beyond the first week of life who have not reached a state of ketosis. In patients with ketosis and in newborn infants, the phenomenon appears to be less readily reversible.

Studies are in progress to correlate these observations with measurements of lactic, pyruvic, and ketoglutaric acid.

Studies of Plasma 17-Ketosteroids in Pregnancy and at Parturition. Dr. Lytt I. Gardner, Syracuse, N. Y.

Concentrations of plasma 17-ketosteroids in pregnant women at term have been measured and found to be significantly lower than adults in the nongravid state. Maternal blood samples were also obtained on hospital entry and at delivery to see if any change had taken place in plasma 17-ketosteroid concentration during the process of labor. There was a clear rise in plasma 17-ketosteroid concentration between hospital entry and delivery in 17 of 22 specimen pairs. In the five women who showed no such rise, there was no obvious explanation. The latter group did not differ as to parity, maternal age, duration of stages of labor, or infant weight from the larger group of 17 mothers. A linear study of plasma 17-ketosteroids in a normal woman before pregnancy, during pregnancy and parturition, and after pregnancy has been made. During pregnancy there was a steady fall of plasma 17-ketosteroid concentration from the prepregnant value to an almost unmeasurably low value about two weeks before delivery. There was a sharp rise of plasma 17-ketosteroid concentration during labor, as noted in the other normal women above, but the level again fell in the immediate postpartum period. For a number of months postpartum, plasma 17-ketosteroid concentration gradually rose toward the initial value obtained prior to pregnancy.

It is hypothesized that during pregnancy there is a lessening of 17-ketosteroid production by the mother's adrenal cortex. As previously reported from this laboratory, the increased umbilical cord plasma 17-ketosteroid values as compared with the maternal peripheral plasma 17-ketosteroid values point to the possibility that some tissue within the fetal-placenta circulation is producing 17-ketosteroids at the time of parturition.

It is possible that the rise of maternal plasma 17-ketosteroid concentration during labor is related to back-diffusion of these steroids from the fetal-placenta circulation into the mother's plasma.

Sweat Electrolyte Studies in Mucoviscidosis. Dr. Harry Shwachman, Dr. Richard R. Dooley, and Milton Stern, Boston.

Further evidence is presented to show that mucoviscidosis is a generalized disease involving the sweat glands as well as mucus-secreting glands. The excessive secretion of sodium and chloride is of such magnitude that this measurement can be used as a diagnostic test. The information derived from this test is as reliable as that obtained from the examination of the duodenal fluid. Its relative simplicity may make it a more valuable test. A practical and simple

procedure for the collection of sweat in infants and children has been devised. The findings in over 500 subjects in the pediatric age range will be presented. No other condition has been encountered with an elevation of the sweat sodium and chloride to the same degree as mucoviscidosis. The elevation of electrolytes in mucoviscidosis is independent of the severity of the degree of pancreatic insufficiency. The test is of special value in studying patients with the typical pulmonary picture of mucoviscidosis who have little or as yet no demonstrable pancreatic enzyme insufficiency.

The Sex Chromosomal Pattern of Teratomas. DR. JAMES B. AREY, Philadelphia.

Barr and his associates have demonstrated a significant difference in the chromosomal patterns of many types of cells in males as compared to females; by means of these differences the sexes can be differentiated. Emery and McMillan have confirmed these findings in biopsies of the skin.

Hunter and Lennox have investigated the chromosomal patterns of epidermal cells in 9 teratomas from males and in 12 well-differentiated teratomas (including dermoid cysts of the ovaries) from females. Whereas the chromosomal patterns of the teratomas in females corresponded to the sex of the host, five of the teratomas in males had a female type of chromosomal pattern.

The present investigation is a continuation of the above studies. Nine teratomas from infants and children, thirteen ovarian teratomas (including dermoid cysts) and two testicular teratomas from adults have been studied. The chromosomal pattern of the epidermal cells of these tumors has been determined. The results of these studies are reported, and their significance with relation to the nature of these tumors is discussed.

A Study of Thromboplastin Generation and Plasma Thromboplastin Content in the Blood of Newborn Infants. DR. ARTHUR E. MCELFRESH, DR. TARO AKABANE, and DR. J. RANDOLPH SHARPSTEEN JR., Philadelphia.

The results of the determination of total thromboplastin and of plasma thromboplastin component (PTC) in newborn infants have not been previously reported. The thromboplastin generation test is a sensitive method for such determinations and requires only small amounts of blood. Prothrombin-free plasma is mixed with serum, platelets, and calcium, and the amount of thromboplastin produced is measured at periodic intervals by utilizing an aliquot of this mixture as the source of thromboplastin in a prothrombin determination. Since PTC, PTA, and the stable prothrombin factor are all removed during the preparation of prothrombin-free plasma but are present in serum, the addition of serum from the same person, from normal persons, or from persons with known deficiencies of one of these factors can be used to measure deficiencies in the blood being tested.

Results of the thromboplastin generation test are reported in 29 infants between 4 hours and 5 days of age. Generation is slow, and the amount of total thromboplastin produced is small when infants' serum is tested with plasma prepared from the same infant or with plasma from a normal adult. Dilution experiments, adding only small amounts of normal adults' serum to infants' serum, show normal generation and thus show that the defective generation is not due to an inhibitor in the infants' sera. The defective generation tends to improve as the infants become older, but none of the studies reported here were conducted in infants more than 5 days of age.

The addition of normal adult serum to infants' plasma results in normal generation, thus correcting the defect noted in the infants' serum.

The separation of PTC and PTA is difficult, since their physical properties are so similar. Serums from the infants were tested by dilution techniques for their ability to correct the defective thromboplastin generation in plasma and serum from a patient known to be deficient in PTC; the defective thromboplastin generation was only partially corrected by the addition of infants' serum. Similarly, the addition of serum from a person deficient in PTC only partially corrected the defective generation of infants' plasma and serum mixtures.

It is concluded that deficient thromboplastin generation is present in infants' blood during the first five days of life. This is in part the result of diminished amounts of PTC in the blood of these infants as compared with normal adults. However, since the addition of serum known to be deficient in PTC partially corrects the generation of thromboplastin in infants' blood, it would seem that some factor in addition to PTC must be concerned; deficient levels of PTA or of the stable prothrombin factor may be involved.

The significance of these findings is discussed in relation to the mechanism of coagulation, both in general and in the newborn period, and to the diagnosis of hemophilia during this period of life.

A New Method of Colloid Analysis. Dr. J. R. Sharpsteen Jr. and Dr. T. Akabane, Philadelphia.

A new method for analysis of colloids in blood is described. The method is based upon electrical charges generated by the colloid following its separation by paper electrophoresis. The charge is quantitated by galvanometric measurement. The results of quantitative determinations of various colloids as determined by this method are now being compared with those obtained by other methods, e. g., refractometric staining, and chemical separation. The method is valuable because of its simplicity and low expense.

The Effect of Tyrosine Administration in Phenylketonuria. Dr. Selma E. Snyderman, Patricia Norton, A.B., and Dr. L. Emmett Holt Jr., New York.

The nature of the metabolic defect in phenylketonuria is now reasonably well established. The hepatic enzyme hydroxylase is missing, as a result of which phenylalanine is not converted to tyrosine. The phenylalanine of the blood rises to extremely high levels, and this amino acid together with a number of aromatic degradation products are excreted in quantity in the urine.

The relation between the symptomatology of the disease and the metabolic error is still a matter of dispute. It is possible that the relation is a coincidental one; the symptoms have also been attributed (1) to an excess of phenylalanine, (2) to toxic metabolic products, and (3) to a deficit of tyrosine. Suggestive evidence of neurological improvement on a restricted phenylalanine diet has been published, but the observations on this point are still equivocal.

We have undertaken to study the effect of supplementing the diet of these patients with tyrosine. Four phenylketonurics between 2 and 6 years of age were given dietary supplement of *L*-tyrosine by mouth in quantities of 1 gm. per kilogram per day. All of these patients exhibited the characteristic blond hair, although they came from families with dark complexion. This dietary supplement resulted in the appearance of dark hair at the root margins. After three months the supplement was discontinued, following which the new hair growing out was pigmented. No evidence of neurological improvement was associated with the tyrosine supplementation. Paper chromatographic studies of the urine showed no change except for an increased excretion of tyrosine.

It is concluded that at least a part of the symptomatology of the disease can be attributed to tyrosine deficit. The observations are, however, compatible with the view that other related aromatic compounds compete successfully with tyrosine in enzyme systems.

Congenital Malformation of the Brain Produced by Exposure of the Pregnant Rat to Rubella Sirus: A Preliminary Report. Dr. Sidney Q. Cohlan and Dr. Shirley M. Stone, New York.

The recognition of the rubella congenital malformation syndrome stimulated investigation of preventive immunologic measures against a disease previously considered benign. Progress in this direction has been limited, in part, by failure of the rubella virus to grow in tissue cultures or to propagate in the laboratory animal. This is a preliminary report of the apparent effect of rubella virus on the developing rat fetus. Pregnant rats were injected intracardially with rubella virus on varying gestation days. The pregnant animals were killed at term. Serial histologic sections of the fetus revealed a consistent congenital malformation of the brain characterized by (1) hydrocephalus, (2) marked narrowing of the cerebral aqueduct and parts of the third ventricle, and (3) adhesions of the meninges to the base of the brain.

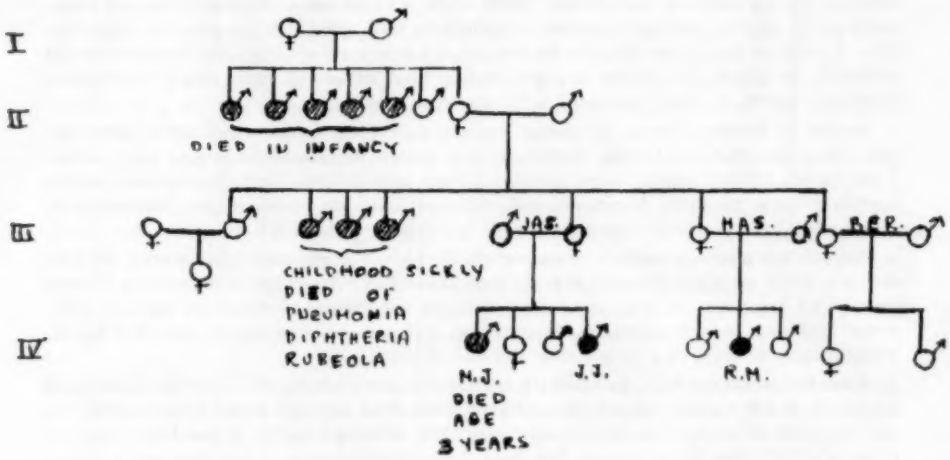
On the fifth, sixth, seventh, or eighth day of gestation, 0.2 cc. of a 1:5 dilution of rubella virus in human serum or distilled water was injected intracardially; comparable amounts of normal human serum or distilled water similarly administered served as controls. Fetal brain malformation was induced most frequently following injection of rubella virus on the fifth or sixth day of gestation. Exposure on the seventh day resulted in a decreased incidence of malformations; no anomalies were observed in animals exposed on the eighth day of gestation. Control brains were all normal.

The brain malformation observed is similar to the anomaly characteristically produced on the 11th day of gestation by other teratogenic agents. The time interval from the day of maternal rubella exposure (5th-7th day) to the apparent time of fetal injury (11th day), may imply a period of virus "incubation," maternal or fetal, prior to developmental insult.

The effect of injecting a mixture of active virus material and γ-globulin prepared from convalescent rubella plasma is being explored. The virus material used in this study was made available by Drs. Saul Krugman and Robert Ward.

Congenital Agammaglobulinemia: A Sex-Linked Genetic Trait and Demonstration of Delayed Skin Sensitivity. Dr. Herbert Porter, New York.

This report comprises a study of a family in which two children, first cousins, were found to have congenital agammaglobulinemia. There is clinical, pathological, and immunological evidence that a sibling who died in 1944 also had congenital agammaglobulinemia. The data obtained indicate that only males suffered from this condition, and that transmission of the trait was through an unaffected female. The hereditary pattern therefore appears to be



similar to that of classical hemophilia. The family tree is shown in the accompanying illustration. The solid circles represent known cases, and the cross hatched circles are possible cases.

Because of the paucity of available data on the ability of these patients to respond to various types of antigenic stimuli, studies were made of the response of R. M. (*a*) to bacterial antigens, (*b*) to viral antigens, (*c*) to a typical chemical antigen unrelated to disease—2,4-dinitrofluorobenzene. This patient was found to have a serum γ-globulin content of less than 10 mg. per 100 cc. by the immunochemical method (determination by courtesy of Dr. David Gitlin). After D-P-T immunization he remained Schick-positive. Separate pertussis immunization failed to stimulate production of specific agglutinins, and the mouse protection test was negative, i. e., no protection. With vaccinia, however, he responded normally showing a typical primary reaction and a typical immune response four months later. Ten weeks after inoculation with BCG. vaccine he became tuberculin-positive; however, the Choucroun test (for tubercle polysaccharide antibody) remained negative. Transfer of the patient's leucocytes to a tuberculin-negative subject with γ-globulin of 0.87 Kunkel units induced local tuberculin sensitivity in the recipient. Attempts to transfer sensitivity to tuberculin by the serum, i. e., Fraction IV-10 of Cole and Favour, thus far have failed, but only small quantities of sera were used. It was possible also to demonstrate induced tuberculin type sensitivity to a chemical agent, 2-4-dinitrofluorobenzene.

These observations are in keeping with the view that sensitivity to tuberculin does not involve the participation of γ-globulin. It seems evident that there is an exact immunologic schism in congenital agammaglobulinemia. The body lacks the ability to produce only circulating

γ-globulin antibodies. The immune response to vaccinia and studies with other viruses may signify the presence of protective serum substances in fractions other than the γ-globulin or may represent production of fixed tissue factors causing local cellular immunity.

Apparatus for the Continuous Recording of Insensible Weight Loss: Clinical and Experimental Applications. Dr. J. G. Frid, Dr. Bernard Combes, Dr. Claude de Menibus, and Dr. George M. Guest, Cincinnati.

Studies of insensible weight loss (IWL) in the past were mainly confined to its relationship to basal metabolic rates. The balances used were delicate, capable of measuring very small weight losses over short periods of time, but only with subjects at complete rest.

For measurement of IWL, particularly during hyperventilation, we have developed a comparatively simple apparatus, employing two types of Toledo Scales: one with capacity 25 kg., the other 95 kg., each with a continuous recording apparatus. A kymograph is arranged to pull "Electrex paper." An Electrex power unit delivers electricity to the indicator needle of the scale and to five needles adjusted to trace calibration lines on the moving paper. Two of the lines are broken by a timer device to indicate minutes and paper speed (usually 1 in. per five minutes). During operation the indicator needle of the scale vibrates with respiration and movements of the subject, making a narrow or fairly wide trail which drifts across the calibration lines. A straight line drawn through the tracing and crossing the calibration channels permits estimation of weight loss within ±1 gm. during long periods of time, despite movements, sometimes violent, as those associated with hyperventilation.

Studies on normal children as control subjects gave IWL values which agree fairly will with those reported by Levine, Anderson, and others for insensible weight loss around 1 gm/kg/hr. Clinical studies have included infants and children with hypothermia, hyperthermia, asthma, paralysis, Mongolism and cretinism, salicylate poisoning, and diabetic coma. As expected, hyperventilation was accompanied by elevated rates of IWL.

Animals are placed in cages with open-mesh floors over a pan containing mineral oil 1 in. deep into which urine and feces fell to avoid errors caused by evaporation of the excreta. Experiments have been done on dogs, cats, rats, monkeys and rabbits to determine rates of IWL under conditions of rest, anesthesia, hypothermia, and with hyperventilation provoked by the administration of drugs such as salicylate and dinitrophenol.

Examples.—Normal IWL in rabbits is usually 0.9 to 1.2 gm/kg/hr. After an injection of dinitrophenol (30 mg/kg.) respirations quickly increased in rate and depth. The maximal rate and amplitude of respirations corresponded with IWL of 4.5 gm/kg/hr. at two hours after the drug. The IWL then fell to normal four hours after administration of the drug and to a subnormal rate, 0.74 gm/kg/hr., at eight hours after the drug.

Normal dogs resting quietly but panting usually have IWL rates of 3 to 5 gm/kg/hr. In a puppy the rate one hour before administration of dinitrophenol was 3.6 gm/kg/hr. Injection of dinitrophenyl provoked extreme hyperventilation, with IWL rate rising rapidly to 19.4 gm/kg/hr., the highest we have observed. Recorded continuously over a period of seven hours, the IWL rate then fell progressively to 5 gm/kg/hr.

Relationships Between the Neonatal Survival of Liveborn Prematures and Various Perinatal Factors Including Specific Hospital Practices. Rowland V. Rider, ScD., Dr. Paul Harper, and Dr. Hilda Knobloch, Baltimore.

As part of a long-term study of premature infants concerned with all live births weighing 2500 gm. or less occurring in Maryland in 1952, details concerning the hospital experience with these babies were obtained. There were 4334 premature infants born in 46 hospitals in Maryland in that year. Specific information was obtained concerning pregnancy, labor and delivery, the infant's hospital course, various aspects of care received in the hospital, and whether the infant survived 28 days. To provide this information, the hospitals completed reports on forms provided for this purpose while the baby was still in the hospital and again at discharge. The survival inforamtion was obtained from these reports if the baby died in the hospital or, otherwise, from death certificates or a one-month visit to the baby's home to confirm survival.

This paper examines the relationships between neonatal (28-day) survival and various aspects of pregnancy and of the infant's course and care in the hospital. Such factors as the following were available for analysis: prepartal visits, complications of pregnancy, duration of

labor and delivery, the baby's condition immediately following birth, age at which feeding was begun, type of feeding, and illnesses of the baby during hospital stay. It was found, for example, that the survival rate was less among babies whose mothers had complications of pregnancy, labor, or delivery than among those who had no complications; that survival was less when feeding was begun before 24 hours than when it was delayed beyond this point, and that in the state as a whole there was little evidence of any association between survival and type of delivery. The effects of anesthesia, analgesia, and other factors listed above were also studied. Some of these statewide findings were unexpected and merit careful analysis. It is necessary in discussing them to take into account birth weight, hospital groupings (according to compliance with accepted standards), and interrelationships among the factors under consideration.

Sarcoidosis in Infants and Children. Dr. John P. McGovern, New Orleans.

A complete review of the world literature on sarcoidosis reveals over 1000 references, including reports of nearly 4000 cases, of which 104 are age 15 years or under. The youngest patient, proved by biopsy, was 2 months old. To an analysis of this group, nine new patients are added. Of the total 113 cases, 28 (24.8%) were 8 years of age and under, and 85 cases (75.2%) age 9 through 15 years at onset.

Organs most frequently involved in infants and children in decreasing order of incidence are: lymph nodes, lungs, skin, eyes, parotid glands, bones, spleen, liver, nervous system (both central and peripheral), and kidneys. Clinical symptoms for the most part are directly attributable to mechanical encroachment upon and displacement of portions of vital tissues, not to so-called "toxic" or systemic reactions.

The histologic pattern is most typical, the involved tissues showing one or more small granulomatous "nests" of epithelioid cells.

Although the etiology of this disease process remains an enigma, studies with Nickerson-Kveim test and results of steroid therapy strongly suggest the role of an antigen-antibody reaction system. That endocrinal changes taking place at puberty exert etiologic or positive modifying influence is suggested by statistical analysis of our data in children.

The use of cortisone or corticotropin (ACTH) in sarcoidosis is recommended only for the control of important, progressively incapacitating lesions due to this disease.

Changes in Total Chloride and the Distribution of Water in Gastroenteritis Following Treatment with High and Low Sodium Chloride Loads. Dr. Donald B. Cheek and Dr. Clark D. West, Cincinnati.

Edema and hypokalemia have frequently been noted during the course of treatment in gastroenteritis. To gain further information as to the nature of these complications, changes in total chloride and the distribution of water were studied in two groups of infants with diarrhea. The first group received 11 to 25 mEq. per kilogram (admission weight) of sodium chloride in the first 24 hours of treatment (average load, 18 mEq. of sodium per kilogram), and the second group, 6 to 7 mEq. of sodium and 8 to 9 mEq. of chloride per kilogram. Both groups received in addition 3 mEq. of potassium and 200 cc. of water per kilogram on the first day. During the second and third days, all cases in both series received maintenance fluid, 3 mEq. of sodium and potassium and 6 mEq. of chloride per kilogram per day.

The volume of distribution of bromide was used to measure total body chloride and to provide an index of extracellular volume. On admission, at 24 hours, and at 72 hours the bromide space was measured together with body weight and serum Na, K, Cl, CO_2, and pH. Changes in body weight were assumed to measure changes in total water. In all cases diarrhea rapidly subsided folowing admission. It was assumed that at 72 hours hydration had been reestablished. The weight at this time was used as the reference point in assessing the total chloride and extracellular volume at the different intervals.

In the patients receiving a high sodium chloride load, studies at 24 hours showed the acidosis to have persisted and the total chloride to average 25% above the expected normal. At 72 hours half of these patients showed an elevation of CO_2 content (range 27.5 to 30.5 mEq/liter) and half of the cases had a low serum K concentration either at 24 hours or at 72 hours. In three patients, the increase in the chloride space at 72 hours was greater than the increase in body weight. In these cases there was, in all likelihood, a failure of rehydration of body cells and an actual subtraction of cell water with treatment. Edema was seen in two of these patients and a mild

convulsion in one. In the other infants of this series the increase in weight was greater than the increase in the chloride space, as one would anticipate.

In the series receiving a low sodium chloride load, normal acid-base balance was restored more rapidly, and hypokalemia and metabolic alkalosis did not occur. Weight gain exceeded the increase in the chloride space at 72 hours, again suggesting a physiologic return of electroyte and water to the cell.

The use of large quantities of sodium chloride (100 to 150 cc. of isotonic saline per kilogram) for initial hydration appears to delay the restoration of acid-base balance and perhaps hampers the return of potassium to the cell, while permitting an increment of cellular sodium content. In some patients the complication of cell water subtraction with edema may arise.

An Evaluation of the Open Carius Method for the Determination of Tissue Chloride. Dr. Donald B. Cheek, Dr. Clark D. West, Catherine C. Golden, and Eleanor M. Doyle, Cincinnati.

In the course of a study correlating the total body chloride measured by bromide with the actual carcass chloride of the rat, a method for determining tissue chloride with a high degree of accuracy was required. The methods selected for trial were the commonly used open Carius procedure (silver-nitrate-nitric-acid digestion) and a method employing alkaline ashing followed by the microdiffusion method of Conway, with titrimetric determination.

Total chloride was first measured with bromide. Four to six mg. of sodium bromide were injected per 100 gm. of body weight, and two hours later blood was drawn from the aorta for serum bromide and chloride concentrations. From these, the volume of distribution of bromide and the total chloride was calculated. The rat was then killed and the carcass clipped of all hair, dried, crushed, and the fat extracted. Finally, the dried carcass was reduced to a homogenous, 60-mesh powder by grinding in a laboratory mill.

The alkaline ash microdiffusion method for the determination of carcass chloride was found to be highly reproducible. Fifty analyses done in duplicate gave an average value of 14.14 mEq/100 gm. of fat free dry solid (FFDS), and the standard error of analysis for a single determination was ±0.19 mEq. Recovery of chloride when added to carcass was complete.

For the open Carius procedure, two methods of digestion with the silver-nitrate-nitric-acid mixture were employed. When digestion was carried out for four hours on a hot plate with frank boiling but without bumping, the values were significantly lower than those obtained by the alkaline-ash-microdiffusion method and were less reproducible. For 25 specimens analyzed by both methods, carcass chloride by the open Carius method averaged 7.5% less than by the alkaline-ash-microdiffusion method, and the standard error of analysis for a single determination was ±0.44 mEq/100 gm. of FFDS. On the other hand, when digestion was carried out by immersion in a boiling water bath for four hours, the values were comparable to those obtained by the alkaline-ash-microdiffusion method and were almost as reproducible. Gentle heating during digestion would appear to be an important factor in the accuracy of this method.

A further check on the methods was provided by comparing the results with the total chloride determined by bromide distribution. Both the alkaline-ash-microdiffusion method and the open Carius method with water-bath digestion gave values agreeing well with total chloride determined by bromide distribution. In 34 rats, total chloride by bromide distribution averaged 8.45 mEq., and by carcass analysis, 8.34 mEq. The coefficient of variation was 5.04%. The data indicate that all of the body chloride of the rat is exchangeable with bromide.

Mucormycosis: Report of a Case Diagnosed During Life and Caused by Rhizopus Arrhizus. Dr. Jerome S. Harris, Durham, N. C.

The present report is that of a child with the typical symptomatology of cerebral mucormycosis in whom the diagnosis was established during life by biopsy and culture. The organism was identified as Rhizopus arrhizus, a member of the family Mucoraceae. Therapy consisted of rigid control of the diabetes, desensitization against the fungus, and the administration of iodides. The child recovered and is the first survival to be recorded.

The literature on "mucor" infections in humans will be reviewed with particular reference to the rare instances of involvement of the nervous system. The typical story is that of a poorly controlled diabetic patient who develops a fulminating orbital or nasal infection and dies in a few days with signs of invasion of the central nervous system. Examination reveals a

necrotizing, inflammatory, and vascular occlusive process in which broad nonseptate hyphae may be seen. Until the present case, diagnosis has not been made during life, nor has the infecting fungus been cultured or identified.

North American Blastomycosis: Report of an Epidemic. Dr. Jerome S. Harris, Dr. N. F. Conant, Dr. D. T. Smith, and Dr. J. G. Smith Jr., Durham, N. C.

During 1954, eleven cases of systemic blastomycosis occurred within a small area in a southern community. Seven children were involved—the youngest being 5 months of age. All patients had pulmonary manifestations. Diagnosis was confirmed by culture of the organism. Therapy proved effective in all cases save one, who died shortly after admission. The course of the epidemic, the methods of diagnosis, and the clinical characteristics of systemic blastomycosis in children will be discussed.

Influence of Fat in Diet on Oxygen Consumption. Dr. T. C. Panos, John C. Finerty, and Richard L. Wall, Galveston, Texas.

Elevation of the metabolic rate characteristically develops in rats fed a fat-free diet. This early observation has been reinvestigated in our laboratory. Serial measurements of growth and basal oxygen consumption were made on groups of male weanling rats fed as follows: fat-free diet alone; fat-free diet plus daily supplement of essential unsaturated fatty acid (100 mg. methyl linoleate); fat-free diet plus daily supplement of saturated fatty acid (100 mg. methyl palmitate); fat-free diet plus daily supplement of a vegetable fat containing approximately 50% linoleic acid (200 mg. cottonseed oil, Wesson); and laboratory chow (Purina). The duration of the experiment was 11 weeks. Oxygen consumption was measured in the fasting, resting state.

Rats fed the fat-free diet showed early growth deceleration and achieved a maximum weight 66% that of chow controls. Supplementation of the basic fat-free diet with methyl palmitate did not affect this pattern of growth, whereas the addition of either methyl linoleate or cottonseed oil resulted in growth indistinguishable from that of chow-fed animals. Transfer from methyl palmitate supplementation to chow diet led to prompt acceleration of growth and achievement of control level within 20 days. Cessation of methyl linoleate supplementation resulted in deceleration of weight gain.

Basal oxygen consumptions of fat-free animals and those supplemented with methyl palmitate were equally and markedly elevated. Transfer from methyl palmitate supplement to chow diet resulted in prompt and pronounced decrease in oxygen consumption. Animals receiving supplement of methyl linoleate or cottonseed oil had basal values entirely similar to those of chow-fed controls. Withdrawal of methyl linoleate supplementation resulted in elevation of oxygen consumption.

Preliminary studies of a similar nature suggest that the results herein reported for rats may prove transferable to human infants. Certain important implications on principles of infant feeding are apparent, since milk mixtures low in fat are commonly used in clinical practice. Increased caloric expenditure reflected by increased oxygen consumption would necessitate a greater total intake of Calories to maintain growth. These results suggest that the use of diets low in fat would tend to disrupt caloric economy and impose an excessive burden on caloric intake, a factor of particular importance in very small infants.

Fat in Diet of Infants in Relation to Caloric Consumption, Growth, and Serum Levels for Specific Fatty Acids. Dr. Arild E. Hansen, Dr. Hilda F. Wiese, Dr. Marjorie Lawlis, Dr. Doris J. D. Adam, Dr. Armond Goldman, and Marjorie Baughan, Galveston, Texas.

With the findings that the blood serum level for two, three, and four double-bond fatty acids reflect the dietary history, nutritional status and essentiality of certain unsaturated fatty acids in experimenal animals, an opportunity has been afforded to study the requirement for one essential fatty acid (linoleic) in small infants. Serum values for dienoic, trienoic, and tetraenoic acids have been found to be remarkably constant in healthy children, whereas in small infants these levels tend to be lower and more variable than for older children. Accurate records of the dietary intake, gain in weight, and the serum level of unsaturated fatty acids were made on seven healthy infants. All the infants were less than one year of age and had been receiving an evaporated milk mixture previous to the study. Diets varying in fat content and fatty acid composition were used. The protein content of all the milk mixtures was the same; this supplied 15% of the total Calories. The basic low-fat diet (A) was composed of powdered skim

milk, carbohydrate, and water, and approximately 1% of the Calories was supplied as fat, with 0.04% as linoleic acid. Diet B was composed of evaporated milk, carbohydrate, and water and had 38% of the Calories supplied by fat, with 0.9% as linoleic acid. Diets C, D, and E were composed of evaporated milk, powdered skim milk, carbohydrate, fat, and water. Fat in these mixtures supplied 33% of the Calories, but linoleic contributed 2%, 3%, and 5% of the Calories, respectively. The usual vitamin supplements were given to make the diets nutritionally adequate, except possibly for linoleic acid. For comparative purposes the serum levels for unsaturated fatty acids in five breast-fed infants were also determined. Growth curves of infants on the low-fat diet were comparable to those when the infants received 33% to 38% of the Calories as fat. However, when calculations were made for the caloric consumption per unit body weight, the infants on the low-fat diets required increased intakes to equal their gain in weight when receiving fat in the diet. In other words, the biologic efficiency of the diets was greater when fat was present in the diet. When the infants were fed on the low-fat milk mixture the serum levels for dienoic and tetraenoic acids decreased markedly even in a period of one week. After one to four weeks on the evaporated milk mixtures (B), these values increased. Invariably, as the values for dienoic and tetranoic acids changes, the change in trienoic acids was in a reverse direction. With the milk mixtures (C, D, E) supplying 2%-5% of the Calories as linoleic acid, changes in all the unsaturated fatty acids of the serum were of greater magnitude but in the same direction as with evaporated milk (B). At no time did the levels for dienoic and tetranoic acid reach those found for breast-fed infants. These studies are being continued, employing diets with wider ranges of fat content and fatty-acid composition.

A Syndrome of Hypercalcemia, Hyposthenuria, and Hypertension in the Postacute Phase of Poliomyelitis. Dr. C. W. Daeschner, Dr. G. W. Clayton, Dr. W. A. Spencer, and G. Housholder, B.A., Houston, Texas.

A reversible syndrome characterized by hypercalcemia, inability to concentrate urine, hypertension, water and salt lability, and resistant potassium deficit has been seen as a complication of the postacute phase of widespread severe poliomyelitis. During a four-year experience in the management of over 250 patients with severe peripheral and respiratory muscle paralysis, eight patients with this syndrome have been encountered.

The medical background of these patients was characteristic and consistent. All were adolescents in the phase of rapid growth when the disease occurred. At the time the syndrome developed all patients were three to eight months beyond the acute phase of poliomyelitis. All had experienced severe poliomyelitis as evidenced by marked reduction in vital capacity, muscle mass, and body weight (average weight loss, 15%-40% of preillness weight). All showed hirsutism, acne, and increased 17-ketosteroid excretion. All had hypercalcuria, and in many hypercalcemia was also present.

Studies of renal hemodynamics and electrolyte excretion, as well as the response to exogenous and endogenous antidiuretic hormone, were carried out. These were compared to similar studies in comparable patients who did not exhibit this syndrome. A moderate reduction (10%-25% below normal) in glomerular filtration rate and renal blood flow were found, but the extent of the observed alteration in renal function was not thought to be of sufficient severity to explain the patients' clinical status. Values for renal vascular resistance were moderately elevated. All patients tolerated water-loading well, with the production of a large volume of dilute urine; however, their antidiuretic response was delayed and incomplete. Electrolyte excretion was not influenced by diuresis or by the ensuing period of antidiuresis.

The etiology of this syndrome is not understood at present. Two possible explanations merit consideration: 1. The previously active individual under circumstances of sudden and complete immobilization develops marked hypercalcuria and hypercalcemia. Hypercalcemia may lead to renal calcium deposition principally in the ascending loop of Henle and distal convoluted tubules. Diminished responsiveness to posterior pituitary antidiuretic hormone and adrenal aldosterone may therefore be expected. The resulting marked polyuria and salt loss leads to a compensatory increase in adrenal aldosterone production. This secondary aldosteronism may then be the major factor in the resistant potassium deficit and arterial hypertension characteristic of this syndrome. 2. The patients exhibiting this syndrome have in common a history of unusally severe fatigue and anoxia. Physical evidence of adrenocortical alarm response is present. Hormones of adrenal cortical origin are known to antagonize the effects of posterior pituitary antidiuretic hormone and lead to polyuria and urinary electrolyte losses.

Renal Hemodynamic Observations in Patients with Cystine-Storage Disease, Amino-Aciduria and Dwarfism (De Toni-Fanconi Syndrome). Dr. C. W. Daeschner, Dr. J. H. Moyer, and Dr. Jorge Awapara, Houston, Texas.

Several observers have noted that children exhibiting the syndrome of cystine storage disease, amino-aciduria, and dwarfism with hypophosphatemic glycosuric rickets show a progressive loss of renal function. This renal insufficiency is usually the cause of death. Postmortem examination of the kidney reveals a severe, generalized disease of the renal parenchyma resembling the end stage of chronic glomerulonephritis.

In the past three years the authors have had the opportunity of performing studies of renal hemodynamic function in four children with this disease. In three patients serial studies were possible, so that a total of 10 renal hemodynamic studies have been performed. The diagnosis of the de Toni-Fanconi syndrome was established by the finding of hypophosphatemic rickets, hyperamino-aciduria, hyper-amino-acidemia, and deposits of cystine crystals in the bone marrow and cornea. All patients showed in addition statural dwarfism, albuminuria, and intermittent glycosuria.

Renal hemodynamic studies were undertaken to study the pathogenesis of the altered renal function. Standard clearance techniques using inulin and sodium paraaminohippurate (PAH) were used. The earliest defect to appear was a marked reduction in the maximum tubular excretory capacity for PAH, unassociated with a reduction in glomerular filtration rate and renal plasma flow. As the patients' disease progressed, the Tm_{PAH} reached minimum values and was then followed by a progressive fall in renal plasma flow and glomerular filtration rate. In the terminal stages all moieties of renal function were severely reduced.

Massive doses of vitamin D (50,000-200,000 units daily) were given to three patients and continued until evidence of hypercalcemia appeared. This therapy produced no significant change in renal hemodynamics.

It is felt that in patients with cystine storage disease the initial renal lesion is a marked reduction in tubular mass transport and that this is then followed by a progressive loss of total renal function. Massive vitamin D therapy has not altered this course of events in the present authors' experience.

Parenteral Reserpine in the Management of Hypertension Due to Acute Glomerulonephritis. Dr. C. W. Doeschner, Dr. J. L. Clark, and Dr. J. H. Moyer, Houston, Texas.

In the past 18 months 22 children with acute glomerulonephritis and hypertension (B.P. above 140/90) have been studied on the pediatric service of the Jefferson Davis City-County Hospital, Houston, Texas. In an effort to select an antihypertensive agent which would be effective and free from significant side-effects, several of the newer hypotensive agents were screened. Preliminary trials suggested that parenteral reserpine fulfilled these criteria. The present report concerns our experience in clinical and renal hemodynamic studies of hypertension in acute nephritis managed with reserpine.

A total of 40 clinical trials were carried out on 22 patients. Seventy-six per cent of the treated patients experienced a significant fall in mean blood pressure (i. e., fall in mean blood pressure of 20 mm. Hg or more) within one to three hours after the intravenous or intramuscular administration of reserpine. This antihypertensive response lasted 8-24 hours. Effective therapy was usually associated with moderate lethargy, and a few patients complained of nasal congestion. No postural hypotension, dizziness, bradycardia, or other side-effects were noted.

In several patients renal hemodynamics and electrolyte excretions were measured before and immediately after a significant hypotensive response to parenteral reserpine had been obtained.

All patients treated demonstrated a fall in renal vascular resistance from the pretreatment or control value. The glomerular filtration rate (clearance of inulin), renal plasma flow (low-level clearance of sodium paraaminohippurate), and the excretion of water and electrolytes (Na and K) showed no consistent change following reserpine therapy. In two patients with oliguria prior to treatment there was a marked improvement in all functions following institution of antihypertensive therapy with reserpine.

The effective single dose of parenteral reserpine varied from 80-150 γ per kilogram of body weight. Individual doses as high as 250 γ per kilogram of body weight were administered without

undesirable side-effects. The antihypertensive response to intravenously administered reserpine usually appeared within one hour, while a fall in blood pressure following intramuscular reserpine was frequently delayed for one and one-half to three hours.

Parenteral reserpine appears to be a safe and effective agent for the treatment of hypertension in the acute phase of glomerulonephritis.

Meconium Staining in Newborn Infants: The Use of the Woods Light in Diagnosis. Dr. M. M. Desmond, Dr. J. E. Lindley, Dr. J. Moore, and Dr. A. Brown, Houston, Texas.

Births associated with meconium-stained amniotic fluid have been studied for a year at Jefferson Davis Hospital. A 10% incidence has been found in a series of 3500 deliveries. The present report is concerned with the recognition of infants exposed to abnormal fluid and the duration of exposure required for visible staining.

Meconium varies in color from mustard yellow to brown to dark green. The latter is the most frequently seen. On exposure to daylight and air for 12-24 hours the color becomes darker and more green in tint. The color of abnormal amniotic fluid corresponds to the color of the infant's meconium. The fluid may be scant and extremely viscid.

In our clinic the nails of normal newborn infants have been exposed to meconium-stained amniotic fluid and solutions of meconium. Staining of nails begins after 4 to 6 hours and vernix after 12 hours of exposure. Placenta and cord assume the color of the abnormal fluid, while nails and vernix are uniformly yellow. The pigment present in such vernix appears to be bilirubin.

The Woods ultraviolet lamp is of value in identifying these abnormal infants. Under the lamp the normal nail border and cord appear bluish-white and the unbroken skin purple. When infants are exposed to meconium-stained amniotic fluids, the first change in the nail is loss of normal color; secondly, the appearance of a tannish shade, and lastly, a striking fluorescence of orange hue at the free border and periungual tissues. Superficial skin shows a similar fluorescence, while that of the umbilical cord and vernix is inconstant.

Babies with intense yellow staining, "collodion skin," etc. (Clifford Types II and III), often have an accompanying circinate, or moth-eaten, type of superficial scaling which is seen on the palmar aspect of the distal phalanx extending toward the palm, on the dorsal metacarpal phalangeal joint, and over the body generally. These areas are sharply defined under ultraviolet light.

The color changes under the Woods lamp appear earlier than those in natural light and disappear more rapidly. The intensities of color under ultraviolet and natural light usually parallel one another, but the fluorescence is more striking and thus more easily graded.

Meconium and meconiun-stained amniotic fluids appear green or brown under the Woods lamp. In two instances meconium specimens have shown a direct orange fluorescence. The source of the fluorescence may be coproporphyrins I and III, compounds which are present in meconium and meconium-stained amniotic fluid.

Comparative Studies on the Absorption and Distribution of Acetyl Sulfisoxazole, Sulfisoxazole, and Other Sulfonamides. Dr. John L. Clark Jr., Dr. Ellard M. Yow, Dr. C. William Daeschner, and Edna Townsend, B.A., Houston, Texas.

The introduction of the more soluble forms of the sulfonamides, such as sulfisoxazole, reduced significantly the incidence of renal complications associated with sulfonamide therapy. However, this greater solubility is accompanied by increase in the bitter taste of the liquid preparation. In an attempt to solve this problem, a poorly soluble acetyl derivative of sulfisoxazole was prepared. Following the oral administration of a suspension of this compound, sulfisoxazole appears in the blood. It has been recommended that the dosage schedule of acteyl sulfisoxazole and sulfisoxazole be equivalent, (593 mg. acetyl sulfisoxazole is equivalent to 500 mg. sulfisoxazole). The present study was undertaken (1) to evaluate the blood levels of sulfisoxazole obtained after the oral administration of sulfisoxazole and of sulfisoxazole and to compare these levels with the sulfonamide level after the oral administration of sulfadiazine and "triple sulfonamide" preparations; (2) to determine the sulfisoxazole level in the cerebrospinal fluid after acetyl sulfisoxazole and sulfisoxazole therapy. Sixty patients on the pediatric ward service of the Jefferson Davis City-County Hospital, Houston, Texas, were given oral acetyl sulfisoxazole, sulfisoxazole, sulfadiazine, and triple sulfonamide. Blood levels and cerebrospinal fluid levels were measured.

Lower blood levels were consistently obtained following the oral administration of acetyl sulfisoxazole than were obtained following an equivalent oral dose of sulfisoxazole. This difference was particularly evident in infants. This was also true when acetyl sulfisoxazole was compared to sulfadiazine and to "triple sulfonamide" following oral administration of equivalent doses.

There was a wider range of variation in the blood levels following acetyl sulfisoxazole therapy than following sulfisoxazole therapy. The concentration in the cerebrospinal fluid was low.

Dosage used in this study was 100 mg/kg. of sulfisoxazole initially and 50 mg/kg. every six hours. The ideal dosage schedule will be discussed.

Fly Breeding in Human Feces from Patients with Paralytic Poliomyelitis. Dr. Russell J. Blattner, Dr. Martha Dukes Yow, Dr. Charles D. Boyd, Dr. Florence M. Heys, and Dr. Fred M. Taylor, Houston, Texas.

The primary purpose of this investigation, conducted over a five-year period, 1948-1952, was to ascertain whether flies of various species permitted to breed in human feces collected from patients with paralytic poliomyelitis and shown to contain the virus of poliomyelitis are capable of retaining the virus, and, if retained, whether virus so acquired will persist during the larval stage, through the pupal, and into the adult stage. From the standpoint of the natural history of poliomyelitis, it seemed of possible significance to determine whether such virus ingested during the voracious larval stage could persist in a dormant pupal stage or be retained by the imago to emergence, thereby constituting a potential reservoir in nature. Such a natural reservoir might account for the wintering of the virus and for survival during interepidemic periods. Factors accounting for increased incidence of poliomyelitis during the summer months, even in semitropical regions, are not fully understood as yet.

Three species of flies were bred successfully in the laboratory in human fecal material; Musca domestica, Sarcophaga bulata, and Lucilia sericata. All flies employed in the virus studies were derived from "clean" stock colonies carried for at least five generations and were shown by animal inoculation (monkeys and mice) to be free from poliomyelitis virus. The stool specimens used in the breeding experiments were collected during the summer epidemic of 1950 from human subjects during a three-week period following definite paralysis in each case. Stool specimens were stored at —20 C until tested for presence of virus, for virus typing, and until material was employed for fly-breeding. Virus strains were identified (tissue culture and typing carried by Dr. C. Arden Miller) by tissue-culture methods as Type I (four instances) and Type III (one instance).

Testing for presence of virus in stool specimens and in fly samplings was accomplished by inoculation of mice and monkeys, rhesus or cynomolgous, principally the latter.

As a check on the methods (detection of virus) followed routinely in the breeding experiments in the preparation of fly suspensions (larvae, pupae, adult flies), adult flies of the stock colony of Lucilia sericata were allowed brief access to and were observed to feed on a dilute suspension of stool material known to contain poliomyelitis virus. Following feeding the flies were removed, stored in a deep-freeze for 48 hours and prepared for animal inoculation in a manner identical with the procedure employed in all fly, pupae, or larvae samplings. Inoculation of cynomolgus monkeys with the suspension prepared from these adult Lucilia flies resulted in paralytic poliomyelitis.

The virus of poliomyelitis was not demonstrated by means of animal inoculations in larvae permitted to feed on and develop in human feces known to contain active virus (Type I, Type II), nor in pupae from these larvae, nor in adult flies emerging from the pupae. The presence of poliomyelitis virus was demonstrated in fecal breeding samples before and after the period of fly breeding, active virus persisting at room temperature in some instances as long as 24 days.

Experimental results are given in the Table.

A Simple Diagnostic Test for Measles. Dr. John C. Macaulay, Dr. Victor N. Tompkins, and Dr. Paul R. Patterson, Albany, N. Y.

The diagnosis of rubeola in the prodromal period has been inadequate. The finding of Koplik spots is limited to approximately 24 hours before the rash develops. The need for early recognition of measles is apparent in the control of epidemics in schools and institutions. A test for early recognition would obviously be of value in the differentiation of febrile illnesses during a measles epidemic and would assist in the disposition of hospital admissions and would make possible the diagnosis of prodromal measles, appendicitis, and encephalitis.

Fly Breeding in Human Feces Containing Poliomyelitis Virus: Specimens Collected from Paralytic Patients

	Fecal Sample	Larvae	Pupae	Adult Flies	Fecal Specimen Remaining After Fly Breeding
Musca domestica	Poliomyelitis virus (strain not typed) Not tested for C-virus	No virus	No virus	No virus	Poliomyelitis virus after 8 days at room temperature
	Poliomyelitis virus (strain not typed) Not tested for C-virus	No virus	No virus	No virus	Poliomyelitis virus after 14 days at room temperature
	Poliomyelitis virus (Type I) Not tested for C-virus	Not tested	No virus	No virus	No virus isolated from specimen following fly breeding
	Poliomyelitis virus (Type I) Not tested for C-virus	No virus	Not tested	No virus	No virus isolated following fly breeding
	Poliomyelitis virus (Type III) Not tested for C-virus	No virus	No virus	No virus	No virus isolated following fly breeding
Lucilia sericata	Poliomyelitis virus (Type I) No C-virus isolated	No virus	No virus	No virus	No virus isolated following fly breeding
	Poliomyelitis virus (Type I) No C-virus isolated	No virus	No virus	No virus	No virus isolated following fly breeding
	Poliomyelitis virus (not typed) No C-virus isolated	No virus	No virus	No virus	Poliomyelitis virus after 16 days at room temperature
	Poliomyelitis virus (not typed) No C-virus isolated	No virus	No virus	No virus	Fecal specimen entirely consumed by larvae
	Poliomyelitis virus (not typed) No C-virus isolated	No virus	No virus	No virus	Fecal specimen entirely consumed by larvae
Sarcophaga bullata	Poliomyelitis virus (not typed) No C-virus isolated	No virus	No virus	No virus	Poliomyelitis virus after 24 days at room temperature
	Poliomyelitis virus (not typed) No C-virus isolated	No virus	No virus	No virus	No virus isolated following fly breeding
	Poliomyelitis virus (not typed)	No virus	No virus	No virus	Poliomyelitis virus isolated following fly breeding period
	Poliomyelitis virus (not typed)	No virus	No virus	No virus	No virus isolated following fly breeding
	Poliomyelitis virus (not typed)	Not tested	Not tested	No virus	Not tested

A simple technique of demonstrating a characteristic multiniucleated epithelial giant cell in the sputum and nasal and conjunctival secretions of children in the prodromal period of measles has been developed and employed in 100 cases of rubeola.

Measles can be diagnosed by this rapid procedure as early as five days before the exanthem develops. The characteristic-appearing cells were not found in a control group of 300 individuals consisting of cases of other exanthemata and viral and bacterial infections.

A Diagnostic Test for Biliary Patency. Dr. Paul R. Patterson, and Dr. John C. Macaulay, Albany, N. Y.

To avoid unnecessary and deleterious exploratory surgery of infants with prolonged jaundice, it is of value to demonstrate that the child does have patent bile ducts.

The following simple procedure has been used to evaluate these infants and to disclose the increased biliary bile flow following cortisone therapy in the so-called "inspissated bile" syndrome.

After the intravenous injection of 0.5 mg. per kilogram of body weight of sulfobromophthalein (Bromsulphalein) (S. B. P.), the infant's stools are collected for the next 12 to 24 hours.

Samples of these stools are streaked across a filter paper wet with any strength sodium hydroxide solution by use of an applicator stick. If any secretion of bile is taking place, S. B. P. will be eliminated and passed per feces and at the site of streaking will be a light lavender discoloration. This denotes the biliary passages are at least patent.

If confirmation is desired, a duodenal tube may be passed and the fluid collected for at least two hours after the intravenous injection of S. B. P. The addition of 1 or 2 ml. of 10% sodium hydroxide to any of the collected duodenal fluid will confirm the presence of S. B. P. eliminated

by the liver by a distinct lavender color. The time following injection of S. B. P. varies with the condition of the liver. Normally, it takes from 20 to 30 minutes for the dye to begin to pass. However, it may require at least one to one and one-half hours in partial obstruction.

If desired, 3 to 5 ml. of 20% sodium dehydrocholic acid (Decholin) may be given intravenously to stimulate the liver flow of bile and to flush the biliary system.

Quantitative Urinary Excretion of Albumin and Formed Elements in Children Drinking Fluoridated and Nonfluoridated Water. Dr. Edward R. Schlesinger, Dr. David E. Overton, and Helen C. Chase, M.Sc., Albany, N. Y.

Fluoridation of public water supplies at a level of about 1.2 ppm of fluoride is an efficient procedure for the prevention of dental caries. While a mass of evidence all points to the safety of water fluoridation, further information is desirable. The present study reveals no demonstrable irritative effects of fluoridated water on the kidneys when the quantitative urinary excretion of albumin, red blood cells, and casts is compared in groups of 12-year-old boys drinking fluoridated and fluoride-deficient water.

The findings in a group of 100 boys, in Newburgh, who had been exposed to fluoridated drinking water for about eight years were compared with the findings in a group of similar size, in Kingston, where the drinking water is essentially fluoride-free. The collection and examination of urine specimens followed the Addis method as modified by Lippman. No limitation was placed on the boys' physical activity prior to collection of the 12-hour specimens.

The mean of the albumin determinations in the Kingston specimens was 32.7 mg., with a standard deviation of 12.3 mg. The corresponding mean and standard deviation for Newburgh was 29.0 and 13.4, respectively.

The average number of red blood cells excreted in the Kingston specimens was 14,700 and in the Newburgh specimens 10,300. In the Kingston group, 60% of the specimens showed a red blood cell count under 20,000 and in the Newburgh group 78%.

The average number of casts in the Kingston specimens was 2819 and in the Newburgh specimens 1900. In the Kingston group, no casts were found in 60% and in the Newburgh group 68%.

The differences found in the results from the groups in the two cities tended to favor the Newburgh children. Statistically, the differences in the excretion of albumin and casts were not significant. No medical significance can be attributed to any of the differences.

A Method for Evaluating Pulmonary Function in Newborn Infants: Measurement of Lung Compliance. Dr. James E. Drorbaugh, Dr. Sydney Segal, Dr. James M. Sutherland, Ruth B. Cherry, M.A., Thomas E. Oppe, M.B., and Dr. Clement A. Smith, Boston.

Abnormal pulmonary ventilation is known to be the commonest cause of neonatal mortality and morbidity. Whatever the underlying pathology, interpretations of etiological factors and evaluation of course, prognosis, and effectiveness of therapy in this highly variable condition requires quantitative and repeated measurement of degree of disturbance in pulmonary function. Among various aspects of pulmonary function thus far investigated (Karlberg, P.; Cook, C. D.; O'Brien, D.; Cherry, R. B., and Smith, C. A.: Studies of Respiratory Physiology in the Newborn Infant: II. Observations During and After Respiratory Distress, *Acta pædiat.*, Vol. 43, Supp. 100, 1954), reduction in lung compliance has been shown to be a major factor in the greatly increased work of breathing required of such infants.

Since compliance represents essentially the ratio of tidal volume to intrapleural pressure change ($\Delta V/\Delta P$) at instants of no flow (i. e., beginning and end of inspiration), its determination necessitates accurate simultaneous volume and pressure measurements. A method has been devised by means of which these measurements are made with little or no disturbance of the infant. A small mask, held by hand over the infant's face, is connected by a flexible tube of wide diameter to an air-filled chamber of about 65 liters' volume. The small pressure changes in this system are proportional to volume changes in the lung and are measured by an electrical manometer. Intraesophageal pressure changes are measured simultaneously by another electrical manometer connected to a polyethylene tube previously placed in the esophagus. In experimental animals and adults, intraesophageal and intrapleural pressure changes are approximately equal. Since the ratio ($\Delta V/\Delta P$) is constant for a relatively wide range of tidal volumes in the individual

subject, volumes larger than the resting mean can be used. Most infants are relatively undisturbed during the one or two minutes required for recording.

By the use of this method, serial measurements of lung compliance have been made on 15 normal newborn infants from as early as three minutes after birth through the first week of life. Since compliance was found to be proportional to body weight, the results are expressed as ml. (of air)/cm(H_2O)/kg. The mean pulmonary compliance of 88 measurements on the 15 normal full-term infants was 1.3 ml/cm/kg. The mean value for the measurements made between 3 and 30 minutes after birth was 1.1 (range 0.6-1.5) ml/cm/kg., and at 5 or more days was 1.5 (range 0.9-2.0). Similar studies of eight infants with respiratory distress (six premature, two term) showed a consistently lower compliance than that of normals at comparable postnatal ages.

In conclusion, it is believed that the method described provides a useful quantitative measurement of disturbance of pulmonary function in the newborn infant, which should contribute to the understanding of etiology and the accurate evaluation of therapy.

RH Isoimmunization Associated with Regurgitation Jaundice Beginning in Utero: A Report of Two Patients. Dr. Marvin Cornblath, Dr. Irving Kramer, and Dr. Alma B. Kelly, Baltimore.

The determination of the total bilirubin in the cord blood of infants with Rh isoimmunization is an accepted guide to treatment. The concentrations of both direct and indirect bilirubin were determined in cord blood of 40 infants with proved Rh isoimmunization. In thirty-five, or 90%, the direct bilirubin was below 3.0 mg. per 100 cc., and in three, 3.0 mg. In contrast the two patients reported below had direct bilirubin levels of 14 and 13 mg. per 100 cc. in cord blood.

One infant with a total bilirubin concentration of 22 mg. per 100 cc. in cord blood had a direct bilirubin level of 14 mg. He died shortly after birth with hydrops fetalis. Postmortem examination showed cirrhosis of the liver, with disorganization of liver cords and a proliferation of fibrous tissue.

The second infant's cord blood had a total bilirubin concentratoin of 24 mg. per 100 cc. and a direct of 13 mg. He was treated with exchange transfusions and then ran the benign course of a mild inspissated-bile syndrome. His direct bilirubin was elevated for two weeks and then fell gradually. At age 14 months, he was well and showed no evidence of hepatic dysfunction. This patient is apparently one with the inspissated bile syndrome which began in utero, and represents a degree of obstructive involvment intermediate between those patients who develop regurgitation jaundice postnatally and those with congenital cirrhosis of the liver associated with erythroblastosis due to isoimmunization. Determination of the bilirubin partition in the cord blood permitted an earlier estimate of his course and called attention to the importance of the liver in excreting bile pigments before birth.

Routine determination of direct as well as total bilirubin concentrations in cord and subsequent blood samples should permit earlier recognition of the occasional obstructive component of the jaundice which occurs in isoimmunization. It would also appear to carry some advantage as a possible guide to treatment, particularly after the first day of life.

The Pathogenesis of Congenital Pneumonia. Dr. Alexander J. Schaffer, Anthony Perlman, M.B., and Dr. Milton Markowitz, Baltimore.

A clinical-pathological study has been made of three groups of infants, 28 liveborn with presumably congenital pneumonia, 28 stillborn with pneumonia, and 30 stillborn with amniotic aspiration but no pneumonia. An attempt has been made to evaluate pathogenetic factors in each case and to draw general conclusions from the aggregation. In this connection a critical analysis of the physiologic observations of Barcroft, Windle, Snyder, and others has been essayed. The histories fall into four groups.

Group A.—Transplacental Infection: Pregnancy and birth histories of four stillborn and eight liveborn infants were normal, except that in the latter group one mother had suffered osteomyelitis in midpregnancy and another had been hemorrhoidectomized two weeks before term. It is suggested that in this group transplacental infection of the fetal lung had occurred.

Complications of Labor and Pregnancy: In 20 of 28 liveborn and 24 of 28 stillborn infants one or more complications had transpired. Most were multiple, few were solitary. Mechanisms can be studied best by consideration of "pure culture" instances.

Group B.—Prolonged Membrane Rupture Time: Excessive time interval between membrane rupture and delivery was the commonest obstetric abnormality, affecting 12 liveborn and 18 stillborn infants. In 3 liveborn and 11 stillborn infants it was the sole abnormality. In these it is suggested that (1) amniotic fluids become contaminated proportionately to the duration of membrane rupture, and (2) amniotic fluid is drawn into some fetal lungs by effective physiological intrauterine respiratory movements. The physiologic evidence pro and con is presented. Significant are the facts that (1) two-thirds of stillborns with pneumonia but only one-fifth of those without gave histories of prolonged rupture time, and (2) that many with a similar history did not develop pneumonia.

Group C.—Circulatory Accidents: A variety of other complications precede fetal pneumonia. The majority are catastrophic accidents, such as abruptio, premature separation, uterine tetany, cord prolapse. These occurred 19 times in the 58 stillborns, but only 5 developed pneumonia, whereas 15 showed massive aspiration of amniotic contents.

In the "pure culture" examples labor or membrane rupture time was not prolonged. Amniotic fluid, therefore, should not have been contaminated, so a different pathogenetic mechanism must be postulated. It is suggested (1) that sudden diminution of fetal blood flow, not anoxia alone, produces exaggerated respiratory movements, (2) that vigorous tactual stimulation may do the same, and (3) that pneumonia follows massive aspiration, but infrequently.

The source of the bacteria producing pneumonitis is unknown, but it seems possible that bacteria may be present in some fetal lungs, perhaps filtered from the blood stream in the course of a transient bacteremia, to produce inflammation only if the lung is damaged or its circulation compromised.

Group D.—Complications of Pregnancy: The mothers of 17 stillborn infants had suffered from toxemia, diabetes, or hypertension. In five there was no other complication. The lungs of only one showed pneumonia; in four there was amniotic aspiration.

These instances differ from Group C in that fetal ischemia, if present, is long continued but small in degree. This might produce some exaggeration of respiratory movement from mid-pregnancy on. Piling up of amniotic residue might result from concentration over a long period of time, as Snyder has suggested, fluid being absorbed, particulate matter remaining. Pneumonia would follow only if bacteria happened to be present.

A Comparison of the Maternal Histories of Three Hundred Eighty-Six Premature and Three Hundred Thirty-Eight Full-Term Infants. Dr. Stuart S. Stevenson, Dr. Kenneth L. Garver, and Dr. Earl Siegel, Pittsburgh.

The maternal histories of the 386 premature infants who were born at Magee Hospital during 1949 have been compared with those of 338 full-term infants. Maternal charts of full-term infants were chosen from a complete file of all still and live births, so that birth dates corresponded as nearly as possible to those of the premature infants. Multiple births in the premature series help to acount for the greater number of premature infants. In addition, whenever the maternal chart of a premature infant was picked from the complete file in selecting the control series, this chart was rejected and no substitute was chosen.

The histories of white and Negro mothers have been analyzed separately. Maternal and paternal age, gravidity, time since marriage, month of infant's birth, legitimacy, serology, maternal disease, maternal hemoglobin level, incidence and indications for Caesarean section, maternal bleeding, placental accidents, length of pregnancy, previous and subsequent abortions and premature births, previous and subsequent full-term stillbirths and neonatal deaths, hospital ward status, and paternal occupation have been compared in the two series.

The maternal histories of those infants born prematurely became of known cause, such as syphilis, have been compared with the maternal histories of infants born prematurely without obvious cause.

There are significant differences between the various groups, which will be discussed.

Osmotic Activity of Tissues. Dr. W. A. Brodsky, W. S. Rehm, J. Appelboom, and W. H. Dennis, Louisville.

Recent experiments have posed a challenge to the validity of the classic concept that cell fluid is isotonic to the surrounding extracellular fluid. Conflicting postulates of cell tonicity have been based on (1) reversible swelling of fresh tissue slices (Robinson, Krebs, Davies, Deyrup) and/or of mitochondria immersed in isotonic media; (2) measures of melting point of solid frozen tissue

(Wirz, Opie); (3) increasing depression (Conway, Sabbatini, Howard) of freezing point of tissue homogenates against time with linear extrapolation of the plot of value of freezing point depression to that of zero time. In view of objections to conclusions derived from all of the forementioned data, the following series of experiments were performed.

Tissues excised from anesthetized dogs were immersed in liquid nitrogen. Then, they were crushed in a Carver Press (at 10,000-20,000 lb/sq. in.), and freezing-point determinations were done on the juice. Alternatively, the frozen blocks of tissue were pulverized to a fine powder in a mortar and pestle after the method described by Conway.

In general, the freezing-point depressions of liver or kidney processed by either method were higher than that of plasma. On the other hand, the osmolarity of RBC mass was the same as that of plasma. The validity of cryoscopic measurements of tissue homogenates was tested by dilution experiments reported elsewhere (*Am. J. Physiol.* **179**:622, 1954). Data suggested that the homogenates in vitro were really hypertonic to plasma.

Increases of homogenate osmolarity with time were noted. The pattern (and the zero extrapolation value) of changing osmolarity was irregular in tissues processed by either method To explain such increases of homogenate osmolarity, analyses of tissue reducing substance, N. P. N., and urea were made. Such analyses indicated that these solutes could account for but one-third of the observed increase of osmolarity. The high initial osmolarity could not be explained by analyses of Na, K, Ca, Cl, Po_4, N. P. N., urea, and fermentable and nonfermentable substances.

Possible explanations of these data are 1. Cell fluid in vivo may be of significantly higher osmolarity than that of extracellular fluid. However, such "internal hypertonicity" requires for its maintenance water pumps or inordinately high hydrostatic pressures in cells or cell membranes essentially impermeable to the osmotic flow of water. 2. Cell fluid in vivo may be isotonic to extracellular fluid. However, freezing in liquid N_2 and pulverizing the tissue may change physical properties of the cell proteins. Such changes may alter activity coefficients of cellular electrolyte or it may break up large molecules yielding a number of smaller, more osmotically active particles. "Explosive metabolism" active at 0 C also might result in some of the observed changes of tissue osmolarity.

The Insensible Weight Loss of Newborns and of Older Infants. Dr. Joseph A. Little, Dr. William A. Brodsky, and Robert Greathouse, B.S., Louisville.

The rate of insensible weight loss of babies during the first few hours of life was but one-third to one-half the usually accepted value, as shown by direct measurements reported herein. Such measurements were obtained with a specially designed scale, capacity of 20 kg. and sensitivity of 1 gm.

Newborn infants, one hour to one month of age, were placed on the scale under known conditons of diet, environmental temperature, and clothing. They were usualy sleeping during test of one to two hours' duration. Insensible loss, measured every 20-30 minutes, was expressed as gm/kg/hr. In all 121 periods of observations were collected during 36 tests on 20 babies.

Results were as follows: (*a*) During the first 12 hours of life, the rate of insensible weight loss (I. L.) varied from 0.4-1.0 gm/kg/hr., with an average of 0.7. (*b*) From the 2d to the 21st day of life, the rate of I. L. averaged 1.4 gm/kg/hr., a value similar to that reported by others. (*c*) Wide fluctuations of data were found for the group as a whole as well as for the individual testing periods in a single infant. (*d*) Crying increased the rate of I. L. to values as high as 4.2 gm/kg/hr. On the other hand, a value as low as 0.3 was noted in a sleeping infant aged 3 hours. The explanation of the low I. L. observed at 2-6 hours of age is not immediately apparent from these data. The role of maternal anesthesia is not excluded. Changes of caloric intake and physiologic weight loss had only small effects on I. L. values.

Since the procedure was simple to perform and innocuous to the subject, it appeared ideally adaptable as a tool for clinical testing. The relationship of I. L. to energy metabolism and to dehydration has been well established by many investigators. Our data suggest that the procedure reported here may be applied to the evaluation of metabolism and/or of dehydration in various disease states. The scatter of observed values was no greater than that of others studying various respiratory and metabolic functions of the newborn.

The influence on I. L. of factors such as fever, dehydration, and respiratory dysfunction was explored in preliminary tests on a few patients.

In summary, the I. L. of normal newborn infants during the first few hours of life was less than one-half of the accepted average value for this age period. After 24 hours of life, the value

of I. L. rose to a mean value of 1.4 gm/kg/hr., a level maintained for at least one month after the initial examination. Wide fluctuations of I. L. were observed in most patients, the maximum range varying from 0.3 to 4.2 gm/kg/hr. The role of prepartum sedation, physiologic weight loss, food intake, and various pathologic factors will be discussed.

Adrenal Steroid Therapy of the Nephrotic Syndrome: An Analysis of Treatment Results in Seventy Children. Dr. Milton Rapoport, Dr. Wallace W. McCrory, and Dr. William Sohn, Philadelphia.

During the six-year period from 1949 to 1955, seventy children with the nephrotic syndrome have been treated with corticotropin (ACTH), hydrocortisone, and cortisone at the Children's Hospital of Philadelphia. In 40 patients treated during the early years of this study (1949-1952) the sole objective of therapy was the induction of diuresis with the removal of edema. Duration of treatment varied from 5 to 19 days in these children (Group I). During 1953 to 1954, thirty children (Group 2) were treated for a longer period of time in attempts to achieve, if possible, complete remisison of the nephrotic syndrome, namely, physiological and biochemical normality in addition to disappearance of edema. When this was not attained by the 28th day, therapy was discontinued by a gradual reduction from full dosage over a three- to four-day period.

Patient responses to therapy were quantitated according to the following four grades:

Grade 1. Complete disappearance of proteinuria, normal blood chemistry, in addition to loss of edema.

Grade 2. Similar to Grade 1, but with residual trace of proteinuria.

Grade 3. Loss of edema, but persistence of proteinuria and biochemical changes in blood.

Grade 4. Persistent edema, proteinuria, and biochemical abnormality.

Treatment aimed at the production of complete remission of the nephrotic syndrome (Group 2 patients) did not achieve this end in all patients, however, it gave more extensive and longer lasting beneficial effects—97% of the children lost their edema, as compared to 78% of Group 1 patients; 67% had complete remission of the nephrotic syndrome at the end of therapy in contrast to 44% of Group 1 patients. Comparison of the status of both groups of children over a one-year period after therapy showed longer duration of all beneficial effects (Grades 1, 2, and 3) in patients of Group 2.

Analysis of the results of treatment for 28 days in Group 2 patients indicated that if a significant effect on the nephrotic syndrome was not obtained after 18 days, prolongation of treatment beyond this time appeared to have no further influence.

Significant data on the influence of steroid therapy on the course of the nephrotic syndrome are available for Group 1 patients only. Treatment of the nephrotic syndrome, based solely on the disappearance of edema as a measure of its effectiveness, appears to have little influence on the ultimate outcome of the illness; the mortality rate in our Group 1 patients followed for a four-year period is 53%.

Whether maintenance therapy, i. e., administration of steroids during edema-free periods, will influence favorably the prognosis of the nephrotic syndrome is unknown. Our data furnish criteria which may be useful in the selection of patients for maintenance treatment. Patients who lose their edema but have proteinuria after an 18-day course of treatment might justifiably be subjected to one of the regimens of maintenance therapy. However, those children experiencing complete remission of the nephrotic syndrome after 18 days of therapy we believe do not require a routine of maintenance treatment. They should be observed, and retreated only when evidences of the nephrotic syndrome (i. e., significant proteinuria) reappear, until they are again in complete remission.

Our data further suggest that a correlation exists between the severity of the renal lesion in a given child with the nephrotic syndrome and the magnitude of favorable response to an adequate (18 days) course of cortisone.

The Ostium Primum Syndrome: A Clinical Study Based on Eleven Proved Cases. Dr. Brian Kieley and Dr. Paul Adams Jr., Minneapolis.

Complete or partial failure of union of the embryological dorsal and ventral atrioventricular endocardial cushions may result in 14 theoretically possible combinations of congenital cardiac anomalies. Six of these would not include an ostium primum and are mentioned only for clarification and classification. Four of these six are purely hypothetical, but isolated cleavage of the

septal leaflet of the mitral valve and possibly isolated cleavage of the septal leaflet of the tricuspid valve have been recognized. Eight combinations would be associated with ostium primum; but, as far as we are aware, only two—persistent ostium primum with cleft septal leaflet of the mitral valve, a diad of lesions, and persistent common atrioventricular canal, a tetrad of lesions—have been generally recognized or reported by pathologists. A third type, persistent common atrioventricular canal without patent interventricular defect, a triad of lesions, will be reported in this paper.

The other five of the eight possibilities associated with ostium primum have not been reported by pathologists and must be considered hypothetical. A suggested classification and nomenclature is outlined in order to simplify and clarify what has previously been a confusing area.

The literature contains much anatomical but little clinical or physiological data concerning these lesions, but the introduction of intracardiac surgery has made preoperative diagnosis important. We have studied 11 cases of congenital cardiac defects associated with persistent ostium-primum, 8 proved by autopsy, all of which were persistent common atrioventricular canal, one without patient interventricular septal defect. Three, who are still alive, were verified by operation alone and may have either A-V canal or some other combination of lesions associated with ostium primum.

Along with the findings to be expected in any defect producing left-to-right shunt, eight features were found to be particularly characteristic of these 11 patients. They are listed in the order of their frequency and importance.

1. Systolic thrill.
2. Slight but definite x-ray enlargement of the left atrium in the presence of interatrial shunt by catheterization.
3. Prolonged P-R interval.
4. The combination of left axis deviation and right ventricular hypertrophy.
5. "Horizontal heart" by electrocardiogram.
6. Systolic murmur at the apex, rather than the left sternal border.
7. Diastolic murmur.
8. Interatrial left-to-right shunt with pulmonary hypertension by catheterization.

The incidence of these eight features in 6 cases of ostium secondum plus interventricular septal defect, proved by autopsy; 20 cases of interventricular septal defect alone, verified by operation, and 25 cases of interatrial septal defect alone, verified by operation, was found to be much lower than in defects associated with ostium primum. The incidence figures in these control groups are to be presented.

We feel that these characteristics when considered in combination are sufficiently specific to make it possible to distinguish ostium primum defects from other septal defects by clinical and physiological methods in most instances.

The results of surgery in these cases by older and newer methods will be presented.

The Study of the Anemia and Movement of Iron in Idiopathic Pulmonary Hemosiderosis. Dr. Leonard Apt and Dr. Myron Pollycove, Boston.

Idiopathic pulmonary hemosiderosis is associated with an anemia of the iron-deficiency type during acute attacks. This is generally interpreted as due to blood loss in the lungs. However, the presence of reticulocytosis, urobilinogenuria, and an increase in indirect serum bilirubin has suggested that the anemia is of the hemolytic type.

Two patients with the disease were studied during periods of remission andexacerbation to determine the mechanism of the anemia. Erythropoiesis and the movement of iron within the body was studied with Fe^{59}. Serial counting-rate measurements were made in samples of plasma and erythrocytes and at sites over a representative volume of bone marrow, liver, spleen, and lung. Erythrocyte survival time was determined by labelling with radioactive sodium chromate (Cr^{51}) and by the Ashby differential agglutination method.

During a period of remission the plasma iron turnover and metabolic pathway of radioiron was normal in that (*a*) the tracer iron was removed from the plasma within a normal period, (*b*) the iron accumulated solely in the bone marrow, and (*c*) over 90% of the tracer iron appeared in the circulating erythrocytes within 10 days. The survival time of the patient's erythrocytes in a normal recipient and the life span of the latter's erythrocytes in the patient was normal.

When the studies were performed during an acute attack there was a normal cycling of radioiron, but it proceeded at an abnormally rapid rate. The plasma iron turnover was two and a half times the normal value. A significant rise in the counting rate over the spleen, which is a regular feature of hemolytic anemias, was not observed. The survival of the patient's chromated erythrocytes was shortened, but loss of blood in the lungs could account for this.

In one patient there were recurrent exacerbations following a radioiron study. These were associated with a sharp rise in the counting-rate measurements over the lung fields; at the same time a decline in the radioactivity in the peripheral blood was observed. Monitoring over the lungs four months later revealed that the counting rates were still high even though only 10% of the original tracer iron concentration remained in the circulating erythrocytes. Together with this apparent redistribution of iron, a hypochromic anemia continued.

The studies indicate that (1) during a remission there is no disturbance in erythropoiesis or erythrocyte survival, (2) during an exacerbation the excessive plasma iron turnover and iron kinetic pattern is characteristic of hemorrhage but not hemolysis; the elevated serum bilirubin level and urobilinogenuria probably results from the absorption of broken-down blood pigment, and (3) iron which is lost from the circulating blood to the lung parenchyma is poorly reutilized despite a continuing iron-deficiency anemia.

The Anemia of Chronic Renal Disease. Dr. Leonard Apt and Dr. Myron Pollycove, Boston.

Both production and survival of erythrocytes were studied using radioactive iron (Fe^{59}) and radiochromium (Cr^{51}) in seven patients with chronic renal disease. In addition, the movement of radioiron within the body was followed by external monitoring. Thus the complete metabolic cycle of iron could be defined. The life span of the patients' erythrocytes labelled with (Cr^{51}) was determined both in the patients and in normal subjects.

Of the patients studied, five had chronic glomerulonephritis, one had chronic pyelonephritis, one had latent chronic glomerulonephritis, and one had polycystic disease of the kidneys. Except for the patient with latent chronic nephritis, all the subjects had moderate or severe anemia, marked azotemia, fixed specific gravity of the urine, extremely reduced glomerular filtration clearances, hyperphosphatemia, acidosis, and variable disturbances in serum electrolytes. The clinical course was stable in five of the patients, progressive in one of the patients with chronic glomerulonephritis, and rapidly downhill in the patient with pyelonephritis.

There were abnormalities in the plasma-iron turnover and/or iron kinetic pattern in all the subjects. The patient with latent chronic glomerulonephritis, who had a mild anemia but no impairment of renal function or disturbance in serum electrolytes, had a definite increase in the plasma-iron turnover rate, with normal movement of iron within the body (plasma to bone marrow to erythrocytes) and 100% incorporation of tracer iron into the circulating erythrocytes. The life span of his erythrocytes in his body was decreased. The other subjects had a low plasma-iron turnover rate, a variable amount of tracer iron (20%-90%) detectable in the circulating erythrocytes and, in three patients, an abnormal intercompartmental movement of iron in that a portion was deposited in the liver. Although the survival of the patients' erythrocytes after autotransfusion was slightly decreased in most instances, it was not a prominent feature of the anemia.

In the patients studied there was no obvious correlation between the degree of anemia and the renal-function tests or blood chemical values. In the five patients with a comparable degree of anemia (Hgb. 6 to 8 gm. per 100 ml.) there was no consistent pattern of iron movement, and the abnormalities in ferrokinetics that were observed could not be correlated with specific changes in renal function or serum electrolytes.

The study indicates that the principal etiological factor in the anemia in these seven patients is impaired erythropoiesis rather than hemolysis. Also, the metabolic pathways of radioiron may be different in patients with a comparable degree of anemia and impairment of renal function.

Results of Medical Management of Coarctation of Aorta Diagnosed in Infancy. Dr. Mary Allen Engle and Dr. Henry P. Goldberg, New York.

Thirteen patients in whom the diagnosis of coarctation of the aorta was made between the ages of 2 weeks and 5 months have been followed during the past seven years. Heart failure

was present in eight when first examined, and common to all but one were symptoms of failure to gain weight and feeding difficulty. Respiratory distress, episodes of cyanosis, and attacks of pallor and perspiration were frequently noted.

The diagnosis was based on the presence of a strong pulse and an elevated blood pressure in an upper extremity, which contrasted with a feeble or impalpable pulse and a low or unobtainable blood pressure in the legs. Blood pressures in the arms ranged from 170/110 to 120/70 mm. of Hg on admission. A systolic murmur was present in all, and a gallop rhythm was detected in all but three of the babies. Roentgenograms revealed enlargement of the left and often of the right side of the heart, and electrocardiograms were indicative of enlargement of one or both ventricles.

Heart failure responded promptly to digitalization and appropriate adjuvant therapy. In most instances digitalis was no longer needed after the age of one year. The hearts did not increase further in size, and the arm blood pressures dropped to normal or near normal levels. Growth in height and weight in all but three with additional complicating lesions proceeded along the normal curve after the first year. Once symptoms disappeared, they did not recur.

During the same period of observation there were eight infants who died between the ages of 2 days and 5 months and at postmortem examination had coarctation of the aorta. Six had been treated for heart failure but without improvement. In only one of these infants was the coarctation uncomplicated by other serious cardiac anomalies, and this infant died at 2 days of age following a traumatic birth.

Our experience with the beneficial effects of nonsurgical management of the difficulties encountered during early infancy by some patients with coarctation of the aorta leads us to believe that medical therapy should be the first choice for such infants and that it is usually effective. Surgery can then be safely postponed until an age when the aorta has reached more nearly adult proportions but has not yet developed degenerative changes.

The Duration of Celiac Disease. Dr. C. P. Katsampes, Dr Augusta B. McCoord, Dr. Estelle Hawley, and Dr. Jack Connelly, Rochester, N. Y.

Twenty cases of celiac disease of chronological ages 7 to 35 years, in whom the diagnosis had been established 6 to 25 years previously, were studied for persistence of their celiac symptoms and absorption of vitamin A ester. Twelve cases still had symptoms of their disease, and

Results of Study of Twenty Cases of Celiac Disease

Duration Disease, Yr.		Peak of Vitamin A Ester Absorption Curve, Oral Dose 7,000 Units/Kg. Body Weight		
Range	No. Cases	Flat or Low (Less Than 100 Units)	Intermediate (100-200 Units)	High (300-516 Units)
6- 9	3	7 * (2) 7 *	10 (1)	.....
10-14	7	11 14 * (3) 33 *†	11 (2) 15 *	11, 11 (2)
15-25	10	16 * 16 21 *† 22 * (7) 27 * (?) 28 * 37	34 * (2) 28 *	27 *(?) (1)
Total cases	20	(12)	(5)	(3)

* Celiac symptoms.
† Sisters.
No. indicates age of patient.

seventeen cases had either poor or definitely diminished absorption of vitamin A ester from the gastrointestinal tract.

The results are summarized in the Table.

From the results, it is concluded that idiopathic celiac disease persists for years, into adulthood. Although the symptoms tended to lessen, they did not disappear completely in a

majority of the cases observed. The continued poor or diminished vitamin A ester absorption showed continued defective absorption or matabolism by the intestinal mucosal cells. The absorption test alone may be useful as a guide to the status of a celiac patient. The results also indicated that the usual and known methods of treatment seldom achieve "cure," if such occurs in this disease. Our results confirmed those of di Sant' Agnese (1953) and extended the known duration of the disease.

The Cooperative Approach in Preparing a Child for Amputation of an Extremity. Dr. Lee Jackson, Cleveland.

There is an awareness among pediatricians of the need for the proper preparation of children for surgery. However, the pediatrician is often uncertain of his role in this regard. Amputation of an extremity, although an infrequent surgical procedure in the pediatric age group, presents problems of a particularly dramatic nature in relation to preoperative management as well as to postoperative rehabilitation.

A single case of a 12-year-old girl submitted to a high amputation of the leg for osteogenic sarcoma will be used as an illustration. The alleviation of her misconceptions, fantasies, and fears was accomplished through the combined efforts of surgeon, anesthetist, nurses, social worker, playroom personnel, psychiatrist and physiotherapist. The pediatrician served as coordinator as well as participant in this program, both preoperatively and postoperatively.

The adjustment of this child to the loss of her leg has been excellent. Undoubtedly her basic personality pattern is largely responsible for this; however, it is felt that the method of approach used contributed materially. The probable importance of this preoperative preparation in relation to a more successful rehabilitation will be discussed.

The responsibility of the pediatrician for initiating such an approach to surgical patients of all types is emphasized.

On the Recognition of Tracheoesophageal Fistula Without Associated Esophageal Atresia. Dr. William K. Sieber and Dr. Bertram R. Girdany, Pittsburgh.

Tracheoesophageal fistula without esophageal atresia is an infrequent congenital malformation. Recurrence of tracheoesophageal fistula is a complication of surgical correction of atresia of the esophagus. Successful ligation of the fistula demands its early clinical recognition.

Previous attempts to outline the tract with roentgenographically opaque mediums have been unsatisfactory. Endoscopic methods of identification are undependable.

Functional patency of the fistula permits flow of air from the trachea and produces marked dilatation of the stomach and intestinal tract. Pulmonary damage results from the reflux of material from the stomach into the respiratory tract. A tube passed into the stomach shows the continued filling of this organ with air under pressure when the infant cries or inspires vigorously.

Sudden and recurrent gross abdominal distention associated with respiratory distress is the cardinal clinical finding in the infant with tracheoesophageal fistula. Failure to thrive and cough and repeated bouts of aspiration pneumonia following surgical repair of esophageal atresia suggest recurrence of tracheoesophageal fistula. Final confirmation of the diagnosis requires definition of the tract.

This paper reports a new and simple method for the demonstration of tracheoesophageal fistulas and describes the clinical picture they present. It stresses the intermittent functional patency of the fistula. Finally, it discusses the mechanism of recurrence following surgical repair of esophageal atresia.

Splenectomy for Hypersplenism in Infantile Generalized Histoplasmosis. Dr. Alex J. Steigman, Dr. Israel Diamond, and Dr. Hugh B. Lynn, Louisville.

Numerous manifestations of histoplasmosis are being recognized particularly in certain endemic areas. The reservoir of infection is believed confined to certain geographic areas. Peripheral extension may ultimately result in more "sporadic" cases outside of the known endemic areas. Altered host conditions, e. g., wide use of broad-spectrum antibiotics which aid multiplication of this organism experimentally, may convert benign histoplasmic infections into more generalized forms.

In its generalized form particularly in early infancy histoplasmosis may be lethal. This report concerns observations made on two desperately ill infants (4½ and 6 months) with generalized histoplasmosis and hypersplenism affecting the three formed blood elements. The clinical diagnosis was supported by cutaneous sensitivity to histoplasmin and recovery of Histoplasma capsulatum from the bone marrow. Splenectomy was associated with prompt noteworthy improvement of the peripheral blood picture and clinical remission. The postoperative bone-marrow cultures became negative.

The frequency and significance of hypersplenism in generalized histoplasmosis is not yet known. Anemia, leucopenia, and thrombopenia, features of the severe generalized lethal form of histoplasmosis, were present preoperatively in these two infants who are believed to be the first ones subjected to splenectomy.

Congenital Hyperthyroidism in Infants Born of Mothers with Graves' Disease. Dr. Virginia D. Weeks, New York.

Pregnancy in mothers with Graves' disease usually results in the birth of a normal infant; nevertheless, various types of thyroid derangement have been reported. The commonest thyroid abnormality is a euthyroid infant with a transient goiter that subsides without therapy. A few cases of hypothyroidism with a transient goiter have been reported, and fewer still are cretins (athyroid). The least common is hyperthyroidism, of which only 6 cases are reported in the literature.

The purpose of this report is to add four more cases of infants with congenital hyperthyroidism born of mothers with Graves' disease. I have arbitrarily chosen 5 weeks of age as the limit by which symptoms or signs of hyperthyroidism develop in order to classify it as congenital.

Some of the interesting features of the 10 cases are as follows: The case reports appeared in the literature from 1910 to 1951. Seven mothers were treated during their pregnancies with strong iodine solution U. S. P., some of these received propylthiouracil. The age at onset of symptoms is variable, irrespective of maternal antithyroid therapy. One case was diagnosed in utero, when the fetal heart rate was over 200/min. One was obvious at birth, two became evident at 3 days, one at 5 days, three at 2 weeks, and two at 5 weeks of age. Exophthalmos was present in six, and the thyroid was palpable in six; two of the latter did not have exophthalmos. Diarrhea occurred in five, irritability in nine, tachycardia in seven, excessive diaphoresis in three, tremor in four, vomiting in two, and cyanosis in two. Serum protein-bound iodine determinations were done in five and were elevated according to Danowski's standards (*Pediatrics* **7**:240, 1951). Four were treated with strong iodine solution U. S. P. with or without 6-prophylthiouracil, the latter for four to six weeks. One infant was not treated, and his protein-bound iodine fell to normal by the eighth week of life (16.8γ at age 17 days, to 7.4γ). Another who was felt to be in thyroid crisis had a protein-bound iodine of 25 and 26γ on the eighth and ninth days of life, received intravenous sulfadiazine and sodium iodide for a 24-hour period, and then was continued on strong iodine solution U. S. P. and 6-propylthiouracil. Radioactive iodine uptake was 62% on the ninth day of life, before therapy was instituted. The duration of symptoms varied. One died on the third day of life from a subdural hemorrhage, five were considered entirely normal by 2 months of age. Symptoms were markedly diminished in one at 3 months, with no further follow-up mentioned. One was normal at 4 months and another at 8 months, and one had subsiding exophthalmos at 2½ years with no further follow-up. Three children were followed for over four years, and their growth rates have been normal. Bone age was not accelerated.

Treatment of Hemolytic Disease of the Newborn at the Chicago Lying-In Hospital: A Comparison of the Results of Standard Small Transfusions with Exchange Transfusion Regimen. Dr. Mila Pierce, Dr. Abbie Lukens, and Dr. Phillip Ambuel, Chicago.

Of 196 liveborn babies affected with hemolytic disease of the newborn delivered at the Chicago Lying-In Hospital in the past 10 years, 117 cases were treated with standard type of transfusions as indicated by the degree of anemia and 79 cases with exchange transfusions. About two-thirds of these 79 cases received one exchange of 500 cc. of blood and one-third of the cases two or more transfusions; practically all of the babies who required multiple exchanges were moderately or severely ill at birth. An analysis of the mortality rate and the incidence of kernicterus in the nonexchanged as compared with the exchange groups offers strong support

for the selection of exchange transfusion for the moderately or severely affected infant at birth. In the 90 cases classified as mild at birth the mortality rate was low with either treatment, but in the 41 babies moderately ill at birth the rate was improved from 14.3% to 3.7% by the exchange regimen, and in the 52 severely ill at birth the mortality rate was 62.4% in the non-exchanged group as compared with 31.3% in the exchanged group. None of 13 hydropic babies were salvaged.

There were 45 deaths, 44 due to Rh and one to A-O incompatibility. Sixteen of the deaths occurred in babies who had received one exchange transfusion, but no deaths occurred in the infants who survived the first exchange in the first few hours of life and who were reexchanged as indicated to control the degree of bilirubinemia. The five deaths due to kernicterus in the exchanged group occurred in cases treated prior to the institution of the multiple exchange regimen. In 24 cases treated with multiple exchanges no death due to kernicterus has occurred; and we have detected clinical evidence of the late neurological sequelae of kernicterus in only one child of this group.

A calculation of the total fetal loss, as stillbirths and neonatal deaths due to hemolytic disease of the newborn in the 10-year period emphasizes again the magnitude of the problem. Further improvement in the mortality rate in the liveborn infants may depend upon a willingness to interrupt pregnancy before term when the maternal history justifies the attempt.

A Longitudinal Study of the Babinski and Plantar Grasp Reflexes in Infancy. Dr. Harry F. Dietrich, Beverly Hills, Calif.

Many past studies, vertical in plan, have established that the Babinski sign is not infrequently present until 2 or 3 year of age in normal subjects. To these valid observations have been appended several surmises:

1. It is generally inferred that in any individual infant the sign may be present at birth and then remain demonstrable for an unpredictable time until it premanently disappears.

2. It is commonly agreed that this early positive sign is due to lack of or irregular myelinization of nerve fibers.

3. It has been stated that the spontaneous occurrence of a Babinski sign in the young infant indicates pathologic changes in the nervous system.

Observations on the plantar grasp reflex were originally confused by the belief that it was the antipodal reaction to the Babinski sign and therefore part of the same reflex. Even after its identity as separate reflex was recognized it was subjected to observation only in vertical studies; these revealed that it was usually present at birth and most often absent by a year of age.

In the present study 86 infants were examined at birth or in the early weeks of life and were regularly reexamined at one-to two-month intervals for the next one or two years. Some infants, for various reasons, were only seen a few times, but in all 711 examinations were done on these 86 babies, with the following results:

1. A spontaneous Babinski sign was commonly seen in normal newborn infants and was not infrequently observed up to 6 months of age; it cannot therefore be considered of pathologic significance.

2. A Babinski sign was ellicited fairly frequently in the newborn period, not uncommonly in the first six months, and occasionally thereafter. Of particular interest are the 29 infants who showed a Babinski sign one or more months after failing to demonstrate one. This observation should raise considerable doubt as to lack of myelinization being the cause of the sign in the normal young infant.

3. The plantar grasp reflex was present with remarkable constancy in the newborn and regularly thereafter until it disappeared at 6 to 12 months of age.

4. The plantar grasp reflex was usually vigorous enough to obscure a Babinski sign when the latter was carelessly tested for.

5. For the first time, the disappearance of the plantar grasp reflex is demonstrated to be related to the age of standing.

The persistence of the plantar grasp reflex beyond its usual duration, or its reappearance, will probably prove to be of pathologic significance. Studies to clarify this point are in progress.

Renal Hyperplasia in Electrolyte Deficiency. Capt. Malcolm Holliday and Dr. Dale M. Schulz, Ft. Bragg, N. C.

This report describes changes in renal tubular histology resulting from long-term feeding experiments with electrolyte-free diet. In addition the effects of specific electrolyte solutions (substituted for water) on the development of these changes and, in certain instances, on the serum and muscle ionic composition are described. Adult rats were fed an electrolyte-free diet for periods of 30, 100, and 200 days. At the end of the study, kidneys were obtained for histologic examination and serum and muscle for chemical analysis.

Sections of kidneys from the 30-day rats were characterized by areas of large pale cells with vesicular nuclei, many in mitosis, in the ascending loops and distal convoluted tubules, which were taken as evidence of regeneration. These changes were similar to those seen in acute alkalosis in desoxycorticosterone acetate (DOCA)-induced potassium deficiency. Muscle potassium in this group averaged 39 mM/100 gm. dry tissue compared to 47 mM/100 gm. for controls. However, there was no elevation of serum bicarbonate. Animals in which isotonic sodium bicarbonate was substituted for drinking water had identical though somewhat more widespread histologic changes, together with a much greater reduction in muscle potassium (25 mM/100 gm. dry tissue) and a marked elevation of serum bicarbonate.

When the period of electrolyte-free intake was extended to 100 days, the animals developed symptoms of inanition. The regenerative hyperplasia increased until projections of cells jutted into the tubular lumen, sufficient, in some, to obstruct the lumen. Muscle potassium was decreased to 32 mM/100 gm. dry tissue. Four of eight animals had an elevation of serum bicarbonate.

A comparable group received sodium bicarbonate developed severe inanition and diarrhea, and all the animals died in the second or third month. The observed symptoms were similar to those previously described in potassium deficiency. No sections were made.

A group given isotonic sodium chloride for 100 days had less intense hyperplasia than those on water alone, although definite changes were evident. Two groups, one receiving potassium bicarbonate and one receiving potassium chloride, had normal renal histology.

The 200-day group on electrolyte-free intake were sickly in appearance, and notable weight losses were observed. The kidneys showed no regenerative hyperplasia, but degenerative changes with dilatation of the tubules and areas of necrosis were seen in many sections. There was elevation of N. P. N. in six of the eight animals.

The histology of 100-day group represents an intense hyperplasia in response to some stimulus. The 30-day group appears to represent these changes in their early phase. Additional interval studies are necessary to evaluate accurately the findings in the 200-day group.

The data confirm a close relation between potassium deficiency and the changes observed in the kidney. In addition, the data permit the inference that alkalosis per se and chloride deficiency or its effect on extracellular fluid volume are contributing but separable factors in the development of these changes.

Circulatory Dynamics of Complete Transposition of Pulmonary Venous Return. Dr. Richard L. Fowler and Dr. Emma Lou Sailors, New Orleans.

Eight cases of anomalous entry of all pulmonary veins into the systemic veins or right atrium have been encountered among more than 800 patients subjected to physiological studies at the Heart Station at Charity Hospital. Catheterization findings in these eight children form the basis of this report.

Five were infants in the first year of life. In four the pulmonary veins converged into a common trunk ("left superior vena cava") which entered the left innominate vein. In one the pulmonary veins emptied into the superior vena cava and in three, into the right atrium.

Four cases showed severe pulmonary hypertension (pulmonary pressure equivalent to systemic pressure); the remaining four showed mild to moderate elevation of the pulmonary pressure. Two of the three children older than one year had only moderately increased pulmonary pressure.

Mixing of pulmonary and systemic venous streams is accomplished in the great veins and right atrium. The majority of this mixed blood is recirculated to the lungs; the entire pulmonary venous drainage is returned as the intracardiac left-to-right shunt into the systemic veins. A certain fraction of the mixed blood in the right atrium escapes by way of the foramen ovale to the left atrium. This fraction (the intracardiac right-to-left shunt) forms the systemic blood flow.

Peripheral arterial blood is composed of blood derived partially from the systemic veins and partially from the pulmonary veins. The fraction representing systemic venous blood is the net or effective right-to-left shunt. Pulmonary arterial blood likewise is composed of blood from the same two sources; the fraction derived from the pulmonary veins and returned directly to the pulmonary artery is the net or effective left-to-right shunt.

The net or effective right-to-left shunt varied from 27% to 47% of the systemic venous return to the heart. The net or effective left-to-right shunt varied between 79% and 350% of the systemic blood flow. The pulmonary blood flow ranged from 140% to 420% of the systemic blood flow.

The preservation of considerable "streaming" of oxygenated blood was indicated in three children and possibly in others by the demonstration of a higher oxygen content in samples removed from the right heart than in samples withdrawn simultaneously from a systemic artery. It has been shown that in fetal life and in cases of atrial septal defect there is often preferential shunting of the inferior vena caval stream through the foramen ovale. The discrepancy in oxygen content of blood removed from the right heart and from the systemic circulation in transposition of the pulmonary veins may be related to the same factor.

Demonstration of severe pulmonary hypertension in three of the five infants under one year and of moderate pulmonary hypertension in the other two emphasizes that anomalies of the pulmonary venous return must be suspected in young infants and confirmed by appropriate studies in order to initiate surgical intervention at a time when the child is still in condition to withstand major surgery and has not yet suffered irreversible damage to the pulmonary vascular bed. Surgery was not successful in the three infants of this group in which it was attempted. Two others died before a surgical attempt could be made.

Experimental Production of Diaphragmatic Hernia: Description of Development and Genetic Application of Findings. Dr. Robert Brent, Rochester, N. Y.

A particular type of diaphragmatic hernia has been reported in the mammalian fetus at term by two investigators. This abnormality consisted of failure of closure of the right posterior portion of the diaphragm at the proper time, allowing smaller or larger portions of the developing liver to herniate into the right thoracic cavity. Anderson observed this abnormality in a certain percentage of fetuses of a particular strain of rats. Wilson was able to produce this malformation in a small percentage of rat embryos born from mothers on vitamin-A-deficient diets.

This same malformation was produced by the author by irradiating 12-day-old rat embryos in utero with 200 to 400 r. As before, this malformation was observed in only a small percentage of irradiated embryos at term. But because the embryos were obtained at daily intervals after irradiation, microscopic sections of the development of the diaphragmatic hernia were obtained for study.

The interesting result of this study was the observation of many of the earlier stages of development of the hernia. These stages will be demonstrated with Kodachrome slides.

The results point to several obvious conclusions, namely, that most malformations have a series of events leading to the final result, and though the early stages may be predetermined genetically in 100% of the cases, the malformation itself may occur rarely on the chance occurrence of the necessary, subsequent developmental events. This fact in itself can explain how we can be mistaken in calling random malformations nonhereditary, when in reality a predisposing dominant or recessive factor is the necessary first step in the expression of a malformation. This genetic trait may be masked by the improbable chain of events necessary to unmask this hereditary trait.

Chronic Peripheral Neuropathy in Childhood. Dr. Lawrence Taft and Dr. Randolph K. Byers, Boston.

Though chronic peripheral neuropathy is a well known entity in adults, it goes virtually unrecognized in childhood. Onset with weakness, ataxia, and deformity of feet or spine is frequent in childhood or adolescence. Erroneous diagnoses of dystrophy or progressive muscular atrophy have been made in all instances coming to our attention, a mistake resulting from the difficulty in sensory examination in children and giving rise to an unnecessarily pessimistic prognosis.

Onset is insidious, with disability out of proportion to the weakness as such. On physical examination loss of sensation to vibration, position sensation, and in lower degree touch and

pain is present in stocking-and-glove distribution. Romberg's sign is often demonstrable before other changes in proprioceptive sensation appear. Tendon reflexes are reduced or absent. With advancing years pes cavus, or kyphoscoliosis or both become important problems. In all, spinal fluid total proteins have progressively elevated over the years. Muscle biopsies show very mild neuronal type atrophy or, early in the disease, normal muscle. Nerve biopsies are not especially helpful early in the disease, although in two of our cases certain observers describe a slight increase in endoneurium or perineurium. Four examples have been seen in the past three years in our clinic.

In none of our cases is the family history positive, nor are the peripheral nerves palpable. Urine examinations for sugar are negative in all. No porphyrins are present in the urine as judged by a change in color on standing. Exposure to lead or alcohol is denied by history and by laboratory findings. Tests for syphilis are negative in all.

The elevated spinal fluid total protein bespeaks an active process undefined in nature, and the relatively stationary clinical state suggests constant repair. This combination of disruption and repair could in the long run result in hypertrophy of nerves and the pathological picture described by Dejerine and Sottas, a condition long regarded as a familial degenerative disease. Consultation of the literature and our material suggests a variety of causes which are still in need of definition. Peruvate metabolism, inflammatory disease, and allergies are some suggested avenues for investigation.

The Prevention of Tuberculous Meningitis. Dr. Edith M. Lincoln, New York.

It is important to determine under what conditions the administration of isoniazid can prevent tuberculous meningitis in children. No one has reported the occurrence of clinical meningitis in a patient on isoniazid therapy or after discontinuing a long course of isoniazid treatment. But information is available on the development of meningitis in patients previously treated with short courses of isoniazid (three months or less), the meningitis occurring one to four months after the use of isoniazid was discontinued. It is necessary therefore to determine the required duration of therapy, the proper dosage, and whether isoniazid prevents meningitis when given alone.

These questions are now being studied by a group of 21 pediatric centers in the United States under the auspices of the United States Public Health Service. The pediatricians are cooperating in a randomized study of children with primary tuberculosis who will all receive either isoniazid in dosage of approximately 5 mg. per kilogram or a placebo. Children will be treated for a year and followed at least one year after discontinuing treatment.

If this study proves that isoniazid used in this manner prevents meningitis we shall possess a sure means of preventing meningitis in known cases of tuberculosis. But we shall still be faced with the problem of the child who develops meningitis before primary tuberculosis has been diagnosed.

A twofold attack will be necessary to solve this problem: applications of all public health measures, including BCG. vaccination, to prevent infection of children with tuberculosis and a program of tuberculin testing to detect primary tuberculosis in its early stage.

Pediatricians and other physicians must adopt tuberculin testing as part of routine health examinations beginning at the latest at 6 months of age; retesting every 6 months through the preschool years, and yearly thereafter through adolescence. Additional tests should be done in the event of unexplained fever or after a history of contact with a tuberculous individual.

Medical Management of Infants with Coarctation of the Aorta. Dr. Ruth Whittemore and Dr. Marjorie Fouts.

During the past eight years, one of us has had experience in following 37 infants who have had coarctation of the aorta. All patients were 2 years of age or under when first observed, the majority of them under 6 months of age. Sex distribution was approximately equal.

Seventeen of these patients died, all of whom had a widely patent ductus arteriosus. The ductus was distal to the coarctation in all but two cases, where it entered a 1 to 2 cm. constriction of the aorta. The clinical diagnosis was made in only five patients prior to death, the majority of whom were in the hospital less than two days. Nine of these patients were under 1 week of age, the remainder under 5 months, at the time of death. The four patients over 3 months of age had other complications associated with the coarctation, such as endocardial fibroelastosis, transposition of the great vessels, or noncardiac difficulties. Both patients who had

endocardial fibroelastosis were admitted with paroxysmal auricular tachycardia and died promptly. Electrocardiograms in most cases showed right axis deviation (right ventricular hypertrophy), although left axis deviation was present in two patients, one with endocardial fibroelastosis.

Of the 20 living patients, three-quarters were first seen prior to 6 months of age, but the diagnosis was made in only one-half at this time. Significant blood pressure changes were not yet present in several of these patients. Eight of the patients had severe cardiac decompensation, three had paroxysmal auricular tachycardia. Other than for poor growth and physical development in almost all of the patients, the presenting symptoms included variable cerebral dysrhythmias, feeding difficulties, dyspnea, and occasional cyanosis below the brim of the pelvis. Electrocardiograms have varied from normal to those with combined hypertrophy in spite of the apparent severity of the defect, but 14 were divided equally between right and left ventricular hypertrophy. Roentgenographic studies have later revealed rather early notching of the ribs in four patients at 16 and 19 months, 3 and 8 years of age.

The natural course of these infants has been of interest, in particular the apparent spontaneous improvement in growth and physical development as well as clinical improvement in many of the infants between six months and one year, and in one or two instances striking improvement again shown during the following year. Operative correction of the coarctation performed in three of these patients between 4½ and 10 years of age improved the growth still further, it is true. The youngest of these patients was submitted for surgery because of lack of growth and weight gain together with difficulty in maintaining compensation. The ductus in this case was still widely patent, but was closed in the older patients. In view of these findings together with those at autopsy, it might be postulated that improvement in growth during the first or second year might coincide with the diminution in size or closure of the ductus arteriosus.

In general, it would appear that the patient whose growth continues satisfactorily and who responds to adequate digitalization (when indicated) may well be able to wait until a more advisable age for corrective surgery. The patient who fails to maintain compensation or whose growth remains stationary probably should be considered for early surgery.

The Chemotherapy of Cancer in Infants and Children: A Progress Report. Dr. Sidney Farber, Boston.

On the basis of 20-year interest in the life history, pathology, and biologic behavior of cancer in early life, and as a consequence of the immediate stimulation derived from progress in our own research concerned with new therapeutic approaches to the problem of disseminated cancer, we organized a broad program of research and care in cancer of early life at The Children's Hospital in Boston, Jan. 1, 1947. The growth of this program led to the formation the following year of The Children's Cancer Research Foundation as a part of The Boston Children's Medical Center. The clinical portion of this program included the application of new chemical, hormonal. or antibiotic agents as part of the total care of infants and children with disseminated cancer after appropriate laboratory studies concerning toxicity and pharmacological properties.

In the first eight years chemotherapy had been given by the staff of the tumor therapy division to more than 1500 patients with advanced or disseminated cancer. Of these 550 were infants and children with acute leukemia.

This paper summarizes the agents employed, the conditions which govern the clinical portion of the program, an evaluation of the effectiveness of chemotherapy, and a statement concerning the most promising present directions of research in the chemotherapy of cancer.

These studies permit the conclusion that the chemotherapy of disseminated cancer represents an important forward step in the treatment of certain disseminated tumors, such as acute leukemia and the neuroblastoma, and that further research in the directions already explored should yield more effective agents with a broad spectrum of usefulness in disseminated cancer in infants and children.

Application of a New Oxygen-Tension Method in Pediatrics. Dr. Bruce D. Graham, Dr. M. U. Tsao, Dr. R. Holland-Moritz, Charles Sloan, and Shirley Sethna, M.S., Ann Arbor, Mich.

A polarographic method for determining plasma oxygen tension has been completed and is being utilized in this laboratory. This is a direct method. Determinations are made on plasma samples which have been separated from the blood cells by a method devised by one of us. Part

of the sample is then equilibrated with a gas of known oxygen tension for calibration. This direct method enables one to obtain the true plasma oxygen tension despite the fact the blood pH, plasma CO_2 tension, and amount of fetal type hemoglobin are variable from patient to patient and unknown at the time plasma oxygen tension is determined. The presence of these variables makes the indirect methods based on oxygen saturation and dissociation curve erroneous. The essential steps in the procedure will be discussed briefly.

Blood oxygen-tension levels have been determined on a number of newborn infants, a fair constancy being obtained. Work is in progress comparing blood oxygen tension and saturation levels when oxygen-enriched air and room air are administered. The significance of this will be discussed.

Applications of this procedure in observations on patients with congenital heart disease are also being made.

The physiologic basis for the need or uselessness of oxygen therapy in this and other clinical conditions is being ascertained on the basis of the partial pressure of oxygen being supplied to and leaving the tissues under various conditions. These results will be reviewed.

Simultaneous Oral, Axillary, and Rectal Temperature Readings in Infants and Children. KENNETH E. AVERILL, DR. JAMES L. WIRSON, and DR. BRUCE D. GRAHAM, Ann Arbor, Mich.

Simultaneous recordings of rectal, axillary, and oral temperatures were obtained in some 60 infants and children on over 120 occasions. Some of the patients had elevated temperatures. The records were made with the use of sensitive thermistors with an accompanying recording system.

The recordings were made under varying environmental conditions, as encountered on the children's ward. Environmental temperature and previous activity of the patient was documented in some cases. The oral probe was placed far back under the tongue. The arm held securely against the side with the probe high in the axilla, and the rectal probe was introduced into the rectum a distance which resulted in the highest reading. All probes were left in place until it was certain that further time or manipulation would produce no increase in the recording. It was found that the temperatures of the rectum, axilla, and mouth approximated each other much more closely than has been reported in the literature to date. Results of the recordings are presented in the paper and the possible clinical application of results discussed.

Electrophoretic Studies of Serum Proteins in Normal and Pathological Newborn. DR. JOSEPH STERNBERG, DR. PAUL DAGENAIS-PERUSSE, and DR. MICHEL DREYFUSS, Montreal, Canada.

Experimental studies with labelled γ-globulins in pregnant rabbit and guinea pig have suggested to us that the placentar permeability for the above proteic fraction is greatly increased toward the last quarter of pregnancy. The γ-globulin not only passes more rapidly into the fetal blood, but its fetal turnover seems to be significantly accelerated during the last period of intrauterine life.

As the problem is of importance for the establishment of the duration of neonatal immunity, a similar study has been projected in humans; as a first step, the comparison between maternal and fetal serum proteins has been investigated. This has been done with the aid of paper electrophoresis, the maternal serum being simultaneously assayed with the fetal sample; thus, the values of fetal serum proteins are established in comparison to those of maternal serum, a better criterion of evaluation of the variations encountered in fetal proteins.

The investigation has been carried out on 102 normal newborn infants immediately after delivery: in a few cases, a second analysis was made two months after birth. The proteins were determined in all the cases by biuret procedure and amido black staining. In 25 cases, the lipoproteins and protein-bound carbohydrates were identified by Sudan black and fuchsin periodic acid staining procedures.

The maternal blood is characterized by a hyperglobulinemia with a low A/G ratio (average 0.79), while the fetal ratio is noticeably higher (1.05 average). In maternal serum, the β and α fractions are significantly higher than in fetal serum, namely 22.6% for β-globulin, 14.1% for α_2- and 5.3% for α_1-globulin in mother, for respectively 14.5%, 11.6%, and 3.6% in fetus. The maternal relative hypoalbuminemia must be considered as compensating the hyperglobulinemia.

The fetal serum is distinguished by a significant increase in γ-globulins, from an average value of 15.3% in mother to 19.0% in newborn. This value is even more significant when the

relative ratios of the various proteic fractions is taken into consideration; the ratio A/G increases from an average of 27.5% in mother to 38.7% in newborn (141% of the maternal value).

The lipoproteins and protein-bound carbohydrates are significantly diminished in fetal serum as compared to those of maternal serum.

In premature infants (26 cases, ranging from 5 to 8 months), the proteic pattern varies greatly according to the age of the fetus; at 5 months the proteic pattern consisted mainly of an important β fraction and a relatively diminished albumin, the γ-globulin being almost absent. After the sixth month, the γ-globulin increases rapidly, the ratio maternal/fetal γ-globulin reaching an average value of 83% at the seventh month and 90% at the eighth month, as compared to 15% in the sixth month. If this fact is confirmed by a larger number of cases, the variation of the above ratio could be taken as an index of the functional age of the premature infant, at least from the immunological point of view.

In erythroblastotic newborn infants (18 cases), the γ-globulin was equal or diminished as compared to that of the mother; in some cases the fetal β-globulin was very increased.

The Renal Tubular Transport of Salicylates: The Vicious Circle of Salicylate Intoxication. Dr. S. A. Kaplan and Dr. P. del Carmen, New York.

The following experiments were carried out in an attempt to provide a rational basis for the therapy of salicylate intoxication, which is the commonest cause of death from accidental poisoning in children under 5 years of age in the United States.

Since it is known that weak bases, for example, ammonia, diffuse more rapidly into an acid than an alkaline urine, it was considered likely that the converse would apply to weak acids such as salicylates. Experiments were therefore designed to test the hypothesis that the inhibition of hydrogen ion secretion by the renal tubules would lead to an increase in the excretion of salicylates, while increased secretion of hydrogen ions would limit the excretion of salicylates.

Sixteen experiments were carried out in dogs in which the clearance of salicylate, glomerular filtration rate, and excretion of sodium, chloride, hydrogen ions, and bicarbonate were measured. The results of the experiments indicate that the back diffusion of salicylate from the tubules is diminished when the secretion of hydrogen ions into the urine is inhibited.

In salicylate intoxication the stimulus to the secretion of large quantities of hydrogen ions consequently leads to excessive salicylate retention which in turn further aggravates the acidosis. A vicious circle is set up which must be broken in order for therapy to be effective.

A carbonic anhydrase inhibitor to break this circle has been investigated in dogs and has been found to increase the excretion of salicylates by 200% to 1000%.

Depression of Tissue Metabolism by Bilirubin, Hematin, and Mesobilirubin. Dr. Richard Day, New York.

Last year the depression of oxygen uptake of fresh rat brain in the presence of bilirubin was reported. This observation has since been reported also by G. H. Lathe. Lathe, however, finds that only brain brei shows this effect, slices being unaffected, which facts have led him to believe that the intact cells escape the action. Our observations were contrary to this. To look into the matter further, whole rat diaphragm has been used, with the idea that cell injury would be minimal in obtaining the tissue. In 10 observations the depression of oxygen uptake averaged the same as with minced brain, being 28% for the diaphragm, and the probability that there was no depression was found to be less than 0.01. Similarly, bilirubin depressed the oxygen uptake of whole yeast cells. The inhibition may be cancelled by the addition of cytochrome C to the solution.

Abelson has suggested that some heme pigment may be toxic in infants suffering from hemolytic disease, and Vogel has interpreted his analyses of kernicteric tissue as indicating that mesobilirubin is the toxic agent. Both of these substances have been tested, the heme pigment selected being hematin. The depression of oxygen uptake of tissues is the same as when bilirubin is used. Cytochrome C also cancels the effect.

Injection of bilirubin every half hour into adult rats whose bile ducts have been ligated results in blood bilirubin levels of well over 50 mg. per 100 cc. Such rats exhibit evidence of toxicity as manifested by sluggishness, convulsions, and death, whereas similarly prepared rats injected only with the alkaline solution used as a vehicle behave almost normally. In vivo observations

are planned with the use of hematin and also with the idea of testing the vivo action of cytochrome C in hyperbilirubinemic rats.

Combination Therapy of Acute Leukemia with Azaserine and Mercaptopurine. Dr. Joseph H. Burchenal, Dr. M. Lois Murphy, Dr. Charlotte T. C. Tan, Dr. Munire Yuceoglu, and Dr. David A. Karnofsky, New York.

The development of resistance to chemotherapeutic agents eventually sets at nought all efforts to control acute leukemia in children. For this reason, combination therapy has been suggested by many as a method of delaying the development of this resistant state.

The compound *o*-diazoacetyl-l-serine (Azarserine), derived originally from a filtrate of a species of Streptomyces by Bartz and co-workers and Ehrlich and co-workers, has been shown by Stock and others to have a chemotherapeutic effect against various types of animal tumors and leukemias. Buchanan and Skipper have shown in pigeon liver enzyme system and in Escherichia coli, respectively, that it acts to prevent the *de novo* synthesis of purines and that, when Azarserine is added to either system, formylglycineamide ribotide accumulates. Presumably Azarserine is acting to prevent the addition of an amino group and the conversion of this compound to-5 amino imidazole ribotide. The *de novo* synthesis of purines appears to be an essential step in the synthesis of nucleic acids by certain leukemic cells. Since mercaptopurine also blocks nucleic acid synthesis but at a different level, presumably at the conversion of hypoxanthine ribotide into the adenine and guanine ribotides, it would be reasonable to assume that the two compounds in combination might give more thorough blocking of the metabolic pathway and therefore demonstrate a synergistic effect. Such an action has indeed been demonstrated in Sarcoma 180 in mice by Clarke and co-workers and also in several strains of mouse leukemia. Because of these biochemical and experimental data, this combination has been studied in 84 children with acute leukemia. When the two compounds are given simultaneously at an oral dose of 2.5 mg/kg. of each there may occasionally be some enhancement of the toxicity of Azarserine. Of 25 children with previously untreated acute leukemia, 18 had good clinical and hematologic remissions lasting 10 to 35 weeks, with a mean of 19 weeks, 1 had a partial remission, and 6 were considered as failures. It should be emphasized, however, that these new patients were a specially selected group, in most of whom it appeared that there would be adequate time for a thorough trial of the combination. Of a group of 14 patients who had been previously treated with mercaptopurine and had become resistant to the drug, 6 very temporary remissions lasting 1 to 12 weeks were achieved, and 8 were failures.

Since the remissions in our series with mercaptopurine alone had an average duration of approximately 12 weeks, it is our feeling that the combination of these two drugs delays the development of resistance to mercaptopurine by from 1 to 4 months and also increases somewhat the incidence of good remissions over that achieved with 6-mercaptopurine alone.

Further Observations on Infantile Idiopathic Hypoglycemosis. Dr. Irvine McQuarrie, Minneapolis.

Clinical and laboratory studies of patients with infantile idiopathic hypoglycemosis have been extended during the past year on newly discovered as well as previously studied cases. The therapeutic response to corticotropin (ACTH) has been uniformly good so far as the fasting blood sugar level has been concerned. More than half of the patients so treated have been able to discontinue hormone medication entirely before the end of the first year without recurrence, while others have required small doses intermittently over a longer period of time for complete eradication of the hypoglycemic tendency. The glycemic effects of growth, lactogenic, and thyrotropic hormones are being studied in these patients, given with or without corticotropin. The effect of the disorder on mental development is also being evaluated.

Studies on Diarrheal Diseases of Infants: Distribution of Enteropathogenic Escherichia Coli Hemagglutinins in Sera of Children of Various Ages and the Basis of a Polyvalent Diagnostic Enterobacterial Hemagglutination Test. Dr. Erwin Neter, Buffalo, Dr. Otto Westphal, Dr. Otto Luderitz, Sackingen, Germany, and Eugene A. Gorzynski, Buffalo.

During the last few years it has been established that the numerous serogroups of Escherichia coli only a few (0111, 055, 026, and 0127) are associated with and in all likelihood responsible for

certain cases of epidemic diarrhea of the newborn and diarrheal disease of infants. Clinical infection by these enteropathogenic serogroups of E. coli in older children and adults is uncommon. It was deemed of interest, therefore, to determine the distribution of E. coli antibodies in children of various ages and to explore their possible placental transfer. Both bacterial agglutination and hemagglutination methods were employed, the latter being far more sensitive than the former (Neter, E.; Bertram, L. F.; Zak, D. A.; Murdock, M. R., and Arbesman, C. E.: *J. Exper. Med.* **96**:1, 1952).

It was found that, out of 323 random sera studied, E. coli 0111, 055, and 026 hemagglutinins were present in, respectively, 7%, 5%, and 13% of infants up to the age of 3 months, 38%, 49%, and 47% of children 3 to 12 months old, 69%, 67%, and 76% of children 1 to 12 years of age, and 93%, 98%, and 93% of older children and adults. The antibody titers in the majority of cases ranged from 1 : 10 to 1 : 80 and only rarely exceeded 1 : 160. In contrast, the conventional bacterial agglutination test revealed the presence of these antibodies in only 3 of these 323 sera, attesting to the greater sensitivity of the hemagglutination method. Parallel titrations of the blood of 26 mothers during delivery and their offspring revealed that passive transfer of these hemagglutinins occurred in only 4 instances, and in these cases the titers of the serum of the mothers were from 4 to 16 times higher than those of cord serum.

That these antibodies are reacting with the somatic or O antigen of E. coli is substantiated by the results of parallel experiments using purified group-specific E. coli 0111, 055, and 026 lipopolysaccharides for modification of the red blood cells. The significance of the data for interpretation of the diagnostic E. coli hemagglutination test and the possible relationship between distribution of these antibodies an age susceptibility to the disease will be discussed.

Further experiments revealed that E. coli 0111, 055, and 026 lipopolysaccharides are simultaneously adsorbed on erythroyctes. It was therefore possible to prepare a polyvalent E. coli antigen for modification of red blood cells, the latter being useful tools for the detection of any of the homologous hemagglutinins. The potential usefulness of this novel approach of devising a polyvalent E. coli, Salmonella, and/or Shigella hemagglutination test for serological diagnosis of enteric infections is being explored and will be discussed.

The Effects of Large Amounts of Vitamin C in Patients with Acute Rheumatic Fever. Dr. Forrest H. Adams and Dr. Robert Ulstrom, Los Angeles.

Several investigators have reported the profound effect of the administration of large amounts of vitamin C on the hormone excretion of normal adults and children. Massell has reported a profound effect of the same vitamin on the acute phase of rheumatic fever; however, most of the evidence for this effect was subjective rather than objective.

This report concerns the effect of large doses of vitamin C (4000 mg/day) followed by corticotropin (ACTH) in patients with acute rheumatic fever. In addition to the usual objective data obtained in patients with rheumatic fever, the following were also determined serially in each patient: the serum mucoproteins, the serum nonglucosamines, the C-reactive protein, the antistreptolysin titer, the urine 17-ketosteroids, and the urine 17-ketogenic steroids. The results and implications of these data will be discussed.

The Turnover of Serum Albumin as Measured by I^{131}-Tagged Albumin in the Nephrotic Child. Dr. Leon Hellman, New York, Dr. Jerome L. Schulman, Baltimore, Dr. Harold Ratner, Dr. Jerome Adesman, Dr. Kurt G. Stern, and Dr. Benjamin Kramer, Brooklyn.

The decline of plasma radioactivity and urinary excretion of isotope have been studied in normal and nephrotic children following the intravenous administration of radioiodine (I^{131})-labeled human serum albumin.

Electrophoretic analyses have demonstrated that administered labeled albumin migrates solely with the albumin fractions of normal and nephrotic serum and is present in the albumin fraction of nephrotic urine.

Plasma radioactivity declines with $T^{1/2}$=10 days in normal and $T^{1/2}$=2 days in nephrotic subjects. These disappearances rates represent the half-lives of serum albumin if administered labeled albumin is a true tracer for endogenously synthesized albumin.

Similar studies have been carried out in normal subjects with I^{131}=labeled human γ-globulin. Observations have also been made concerning the urinary excretion of lipids and steroids in an attempt to define the origin of nephrotic hypoproteinemia and hypercholesterolemia.

Late Effects of Exposures to the Hiroshima Atomic Bomb Among Individuals Now Nine to Nineteen Years of Age. Dr. Robert W. Miller, Hiroshima, Japan.

The pediatrics department is conducting a search for late effects of exposure to the atomic bomb in individuals who were embryos, fetuses, infants, or children at the time of exposure.

Among 4407 patients examined in 1954, the youngest were in utero on Aug. 6, 1945. The oldest were then 10 years of age. Those closer than 1800 m. to the bomb are considered to have been exposed to ionizing radiation. Those between 3000 and 3500 m. are considered nonexposed. Over 55% of the exposed and over 40% of the nonexposed survivors in each age category were examined in 1954.

Among those exposed in utero who were first examined in 1954, none had mental retardation associated with head circumference more than three standard deviations below the average for the general population. Previously, eight patients with this combination of congenital malformations had been found in Hiroshima. All these children were born of mothers who were within 1210 m. of the hypocenter. All but one of these women definitely epilated. The children were between the 7th and 15th week of intrauterine life at the time of exposure.

One new case of leukemia (chronic myelogenous) was found in the past year. Since 1949 the onset of leukemia has occurred in 18 patients under the age of 19 years who were within 2200 m. of the hypocenter. No cases have been discovered among those in the same age range who were between 2200 and 5000 m. There were seven cases of leukemia found beyond the greatest distance at which microcephaly with mental retardation occurred. This provokes consideration of the thresholds for the two abnormalities and their possible relationship to exposure to ionizing radiation.

No new cases of hypoplastic anemia were found in 1954. Since 1949, two cases of this disease have been observed in the exposed compared with one case among the nonexposed group.

Forty patients had hemoglobin levels below 10.0 gm., occurring with similar incidence in the exposed and nonexposed groups.

Cataracts among those exposed early in life consist only of minor defects of the lens. None impair vision of these patients.

A progressive rise with age in the incidence of myopia and/or astigmatism was observed in the nonexposed group. However, those closer to the hypocenter than 1800 m. who are now 16-19 years of age have a significantly higher incidence of these eye defects than do the nonexposed of the same age group.

Those closer to the hypocenter are not more susceptible to chronic purulent otitis media than those who were distant. Hematologic values for both groups were similar, indicating that the hematopoietic system of the exposed individual is not especially sensitive to this infection as revealed by these determinations.

One brain tumor, type unknown, was diagnosed among the pediatrics (in utero) group in 1954.

Of 4407 patients examined in 1954, 29 have injuries (other than well-healed scars) which are sequelae of the blast or thermal energies of the bomb.

Chronic Regional Enteritis and Growth Retardation in Childhood. Dr. Edna H. Sobel, Boston, and Dr. Frederic N. Silverman, Cincinnati.

While the endocrine system is often involved in growth retardation, it is rarely the primary basis of dwarfism. As disease of other organ systems is a more frequent cause, careful search for a remediable disorder is indicated in the evaluation of every dwarfed patient. Although renal disease may manifest itself clinically only by growth failure, disturbance of other systems (cardiac, pulmonary, hepatic, intestinal, or skeletal) is usually readily evident when it is so severe as to impede growth.

Regional enteritis in childhood is commonly an acute or subacute disease, which may be confused with appendicitis. This report concerns two children with chronic regional enteritis in whom the primary complaint was of slow growth and maturation. Both were at first thought to have primary hypopituitarism, since skeletal and sexual maturation were retarded and there was laboratory evidence of diminished gonadotropin excretion. One of the patients, a 13-year-old girl, failed to respond to thyroid hormone and had sufficient impairment of appetite and mood to suggest the possibility of anorexia nervosa. Her serum-protein level was low, and she had a history of an episode of severe crampy abdominal pain occurring three years previously. The other patient, a 15-year-old boy, had chronic anemia and occasional nausea, vomiting, and diarrhea.

In each instance roentgen examination of the gastrointestinal tract, undertaken because of the rather minor digestive symptoms, revealed previously unsuspected regional enteritis. The first patient was treated surgically, as she had a jejunocolic fistula. Thereafter she began to grow rapidly and to mature sexually. Despite efforts at psychotherapy a relapse occurred, and she died after a second operation was performed to relieve a recurrent partial intestinal obstruction. The other patient is at present on medical management.

The clinical, radiographic, and pathologic features of regional enteritis will be presented with comments on its possible relationship to growth retardation.

Outlook for Pregnancy in Women Immunized to Rh. Dr. Edith L. Potter, Chicago.

Twenty years experience with Rh and erythroblastosis at the Chicago Lying-in Hospital is reviewed. There have been approximately 350 pregnancies in which the mother has been immunized to D. or c. Especial attention is paid to the effect of the pregnancy on the mother, prognosis for the outcome of the pregnancy, and outlook for future pregnancies. Pathology of erythroblastosis as exemplified by 140 postmortem examinations is briefly summarized.

Spread of Poliomyelitis: Respiratory or Excremental Pathways? Dr. Robert Ward and Dr. Charles C. Chang, New York.

The modes of transmission of poliomyelitis are unknown. One group believes that the disease is contracted like measles and other respiratory infections. Another believes that it is spread via intestinal-oral channels frequented by typhoid fever, dysentery, and infectious hepatitis. The various arguments pro ond con will be discussed. Ports of entry and departure are helpful in determining the means of transportation. We have tried to find out if poliomyelitis virus is commonly eliminated from the respiratory tract. Nineteen patients in the first three days of illness blew through glass tubes into tissue-culture nutrient fluid. This was tested later for polio virus in cultures of monkey-kidney cells. Virus was also looked for in nose, throat, and rectal swabs. It would appear that the 13 patients with detectable virus in the oropharynx stood the best chance of eliminating virus from the mouth. Virus was found in the exhalations of one such patient, a 22-year-old man with bulbar poliomyelitis which proved fatal. Virus was also recovered from the nose swab of this individual and from that of one other. It was found only in the rectal swab of six additional patients. There is scant evidence that polio virus is readily eliminated from the upper respiratory tract. It therefore does not seem likely that poliomyelitis is often transmitted in the manner of common colds, measles, and other respiratory infections.

Influence of Surgery on Renal Water and Salt Excretion in Infants and Children. Dr. Philip L. Calcagno, Dr. Mitchell I. Rubin, and Dr. Walter S. A. Singh, Buffalo.

There is an increasing trend in the management of young infants to restrict water and salt in the immediate postsurgical state. Numerous studies in adults indicate that a postoperative retention of water and salt occurs and is said to be attributable to renal dysfunction. Since it is known that dehydration imposes certain physiological handicaps, it seemed important to investigate whether there was a need to restrict fluids and salt in the postsurgical state.

Our initial observations showed a rough correlation between fluid intake and urine volume postoperatively, and in addition there was an inverse relationship between urine volume and urinary osmolar concentration. With these preliminary observations suggesting that dehydration may have been a significant factor in producing the postsurgical oliguric state, studies were planned to precisely determine whether there was an alteration in the renal capacity to excrete water and salt in the postsurgical state.

A group of 70 infants and children undergoing various types of surgical procedures (pyloroplasty, bowel resection, biliary atresia repair, herniorrhaphy, cardiac shunt operations, craniotomy for subdural hematoma, etc.) were included in this study. Since both glomerular filtration and tubular function are involved in the renal excretion of water, these two mechanisms were investigated. The glomerular filtration rate (using the inulin constant infusion technique) was determined before and after surgery to define whether intrinsic glomerular dysfunction existed as a mechanism in the production of oliguria. In most of the children there was no alteration in the glomerular filtration rate following surgery. The tubular regulation of water excretion was tested by a response to a water load (water diuresis) administered intravenously (525 ml/square meter of a 2½% dextrose in water solution within a period of 10 minutes). Urine collections were made at half-hour intervals over a period of two hours. This test was performed both before and after surgery. Control dehydration (similar in extent to that occurring during

the starvation period used commonly in the preparation of surgical patients) was imposed on four patients to determine the influence of fluid deprivation on water diuresis. This restriction resulted in a marked reduction in water diuresis. Surgical patients similarly dehydrated preoperatively in preparation for operation and coupled with the dehydration from fluid losses in the operating room (patients lost weight at about 300 gm/square meter/hour) showed a response to the water-load comparable to the nonsurgical "controlled dehydration" patients. In another group of infants where dehydration was prevented by hydration both before and during surgery, the diuretic response to a water load was similar to the presurgical test.

The second phase of this study was concerned with the rate of excretion of sodium postoperatively. In the adult literature retention of sodium is said to occur. For this purpose a 3% sodium chloride solution was administered intravenously (525 ml/square meter within a half hour). Urinary excretion of sodium was followed for three and one-half hours after the completion of the infusion. The urinary excretion of sodium presurgically in this group of infants was about 25% of the administered sodium load, a value quite comparable to that of adults. The infants studied postsurgically showed no defect in renal excretion of sodium.

Conclusions.—1. Our data suggest that postoperative oliguria in the infant and child is in a large measure due to dehydration.

2. There is no apparent intrinsic renal dysfunction in excreting either water or sodium.

3. The data refute the need for inducing dehydration on the basis of renal dysfunction in the postsurgical state.

Acidosis and Hypoglycemia in Infants of Diabetic and "Prediabetic" Mothers. Dr. H. S. Reardon, Dr. S. H. Field, and M. L. Baumann, B.S., Philadelphia.

In a series of 27 newborn infants of diabetic and "prediabetic" mothers, there was a definite increase in the CO_2 gas tension (pCO_2) in the plasma of all the infants (five) who died. The increased pCO_2 was associated with a low plasma pH. The plasma pCO_2 remained within the normal newborn range in 20 of the infants who survived.

In 11 of the 27 infants, blood glucose was determined at 4 hours of age. Seven of these infants had blood glucose values below 15 mg. per 100 cc. Four of the seven infants died; the blood sugar level of the other infant who died is not known. The three infants with hypoglycemia who survived had plasma values for pCO_2 within the normal newborn range. Four infants with neonatal values for plasma pCO_2 and blood glucose within the normal ranges had uneventful neonatal courses.

It would appear from data available at this time that within a few hours of birth prognostic information can be obtained from the level of the plasma pCO_2. The possible significance of an associated hypoglycemia will be discussed.

Studies on the Abnormalities of Copper Metabolism in Hepatolenticular Degeneration (Wilson's Disease). J. A. Bush, J. P. Mahoney, C. J. Gubler, H. Markowitz, G. E. Cartwright, and M. M. Wintrobe, Salt Lake City.

Observations in this laboratory and elsewhere have demonstrated a number of alterations in copper metabolism in patients with hepatolenticular degeneration (H. L. D.). In normal subjects 93% of the serum copper is bound to ceruloplasmin, an α_2-globulin. The remaining 7% is bound to albumin. In H. L. D. the total serum copper is low due to a reduction in ceruloplasmin. The copper bound to albumin is increased. Patients with H. L. D. are in positive copper balance, the concentration of copper in the tissues is increased, and the urinary excretion of copper is elevated.

In 14 patients with H. L. D., ceruloplasmin values (measured by an immunologic technique, ranged between 2 and 19 mg/100 ml. (normal 27-38 mg/100 ml.). There was no correlation between ceruloplasmin concentration and duration or severity of disease.

After oral administration of Cu^{64} to three normal subjects, a mean of 76% of the dose was recovered in stools and 0.1% in urine. Three patients with H. L. D. excreted 55% in stools and 3% in urine. Maximum plasma activity (one to three hours) was greater in the patients than in the control subjects. At this time the activity was in the nonceruloplasmin fraction in both groups. In the patients there followed a slow decrease in plasma activity, and little Cu^{64} entered ceruloplasmin. In normal subjects, following a brief decrease, the activity increased gradually due to incorporation of Cu^{64} in ceruloplasmin. The administration of potassium sulfide by mouth along with Cu^{64} effectively inhibited the retention of Cu by the patients.

Following the intravenous administration of Cu^{64} to three normal subjects, 13% of the dose was recovered in stools and 0.3% in urine. Three patients with H. L. D. excreted 2% in stools and 5% in urine. Two patients with hepatic cirrhosis excreted 9% in stools and 1% in urine. Normal subjects cleared injected Cu^{64} from the plasma more rapidly than patients with H. L. D. Twenty-four hours after injection, most of the activity in the plasma of normal subjects was in ceruloplasmin, while in patients with H. L. D. the activity remained bound in albumin. Body-surface counts over the liver of the patients failed to increase to a degree comparable to that observed in normal subjects.

These data show that the incorporation of Cu^{64} into ceruloplasmin is impaired in H. L. D. Since one of our patients had more than half the normal quantity of ceruloplasmin, this finding is explained best by the existence of an excessively large "labile copper pool" in addition to deficient synthesis of ceruloplasmin. The accumulation of copper in the tissues of patients with H. L. D. appears to be due to both increased absorption from the gastrointesinal tract and decreased excretion by the liver. The latter abnormality is independent of liver function, since patients with cirrhosis do not exhibit a similar defect.

Ventricular Septal Defect with Pulmonary Stenosis: A Spectrum. Dr. Alexander S. Nadas, Dr. Walter T. Goodale, and Dr. John M. Craig, Boston.

The tetralogy of Fallot until recently has been regarded as an anatomically fixed lesion, consisting of pulmonary stenosis, ventricular septal defect, overriding aorta, and right ventricular hypertrophy. With the introduction of cardiac catheterization and angiographic techniques, the dynamic physiological concept of pulmonary stenosis with a right-to-left shunt through a ventricular septal defect was substituted for the static, anatomical idea.

The purpose of this paper is to present the entire spectrum of the possible physiological and clinical situations which may arise from the anatomical combination of ventricular septal defect and pulmonary stenosis.

The classical tetralogy of Fallot picture consists of an obstruction—infundibular or valvular—at the right ventricular outflow tract, resulting in a pulmonary resistance in excess of the systemic resistance a right ventricular pressure equal to systemic arterial pressure, and a moderate right-to-left shunt through a ventricular septal defect. These patients are cyanotic at rest, they have severe exercise intolerance, and they squat. The pertinent clinical findings include a stenotic systolic murmur, a diminished pulmonary closure, right ventricular hypertrophy electrocardiogram, and a small heart with diminished pulmonary vasculature by x-ray.

On the other extreme of the spectrum is the picture of a left-to-right shunt through a ventricular septal defect, with mild pulmonary stenosis. The pulmonary resistance in these patients is significantly lower than the systemic resistance. The right ventricular pressure is below the systemic arterial pressure and a sizeable left-to-right shunt through a ventricular septal defect occurs. Cyanosis in these cases is absent, exercise intolerance is mild, and they never squat. On auscultation, the pulmonary closure is relatively normal, and, in addition to the typical stenotic murmur, an apical, diastolic rumble is also present. The electrocardiogram commonly but not invariably shows right ventricular hypertrophy. By x-ray the heart is large and the pulmonary vasculature is engorged.

Patients representing intermediate stages between these two extremes have also been encountered. In some children a delicate balance exists between right-to-left and left-to-right shunt, so that cases clearly belonging to the left-to-right shunt group, at rest, will exhibit the characteristic symptoms and signs of a tetralogy of Fallot on exercise. Finally, we have also seen patients who, in early infancy, were logically diagnosed as having a ventricular septal defect with left-to-right shunt but who consequently, in later childhood, presented the classical picture of tetralogy of Fallot.

Individual examples of these situations with pathological, clinical, and physiological data will be presented, and the therapeutic implications will be discussed.

The Use of the Electroencephalogram in the Evaluation of Hearing in the Preschool Age Child. Dr. Arthur J. Derbyshire, Dr. Paul V. Woolley Jr., Dr. Mary D. McDermott, and Alan R. Fraser, M.A., Detroit.

The neurophysiologic apparatus for communication involves peripheral end-organs communicating by neuropathways to a central area of reception, followed by integration, which leads,

in turn, to symbolism and concept, all resulting in a motor pattern of movement, speech, or visceral change.

Two methods of appraising this chain of events, when the end-organ involved is aural, are the Standard Audiometric Threshold and the Psychogalvanometer Skin Resistance Test. Since the former depends upon sound input and somatic motor output, it gives the over-all characteristics of the communication system and thus a summation of defects in the peripheral system (ear or nerve deafness), the central apparatus (aphasia or "brain damage"), and ability of output through the somatic motor system (age of child, cerebral palsy, etc.). The latter utilizes, likewise, sound intake, central conditioning, but output through the visceral motor system, and thus is vulnerable as a test at the levels of conditioning and visceral motor function, such as in severe psychogenic disturbances.

Our objective therefore has been an effort to develop a technique of measuring which would, first, differentiate between the peripheral and somatic motor system failure (as with the Standard Audiometric Threshold) and, secondly, not depend upon central conditioning or the visceral motor system output (as with the skin resistance). We have sought especially a method which would be accurate, rapid in application, saving in manpower, and yet, would provide findings repeatable within workable limits.

It has been known since the early work of Davis that aural stimulation results in detectable modification of an existing electroencephalographic pattern, and this has lead to our efforts to quantitate and qualitate such responses. In all, both click and tone stimulation has been presented to 150 children under conditions of sleep. These subjects have varied in age from 3 months to 13 years, and our observations have been controlled by Standard Audiometer Threshold Tests where feasible and otherwise by close clinical school, and home, observations.

Sleep has been obtained by secobarbital (Seconal) sodium sedation while under testing conditions and stimulation both by clicks and by puretones of five seconds' duration recorded. The former gave rise to "K patterns" as described by Davis, while the latter produced three electroencephalographic changes: (1) an "on effect," (2) continuing change, and (3) an "off effect"; at least two of these changes were considered necessary to grade a test as positive. The on-and-off effects were usually reduction of voltage or appearance of K formation. The continuing change could be either an increase or decrease in voltage. All patterns of response were as variable as the depth of sleep and showed no areal localization. The intensity at or above which there was response at least 50% of the time was used to plot threshold curves. The points on these curves agreed with those obtained through Standard Audiometric Threshold testing with an average variation of only 18 db., plus or minus. An individual procedure requires two and one-half hours by a single operator plus an additional hour for interpretation and recording.

The arousal response to the electroencephalogram uses sound for the peripheral input but records directly changes in central pattern rather than utilizing a true output pathway. It therefore sees distortions peripherally or centrally, and criteria are available for distinguishing these two types. Greatest usefulness is obviously in studying children with "aphasia." "brain damage," or visceral motor incapacities. It is offered as an aid in the evaluation of the hearing part of the apparatus for communication in children between 3 months and 4 years of age. When used in conjunction with good clinical and audiologic observation, it has been of value to us in pointing out routes for further evaluation of infants and children with defects in communication.

News and Comment

ANNOUNCEMENTS

A. M. A. Annual Meeting, Chicago, June 11-15, 1956.—The 105th Annual Meeting of the American Medical Association will be held in Chicago, June 11-15, 1956, with a full program of lectures, television, motion pictures, and scientific exhibits.

The lecture program for each Section is prepared by the Section Secretary, and prospective participants should communicate as soon as possible with the Secretary of the Section before which they hope to read a paper. Application blanks for space in the Scientific Exhibit are now available and may be obtained from the Section Representative to the Scientific Exhibit.

Section on Pediatrics

Secretary: Wyman C. C. Cole Sr., M.D., 3001 W. Grand Blvd., Detroit 2.

Exhibit Representative: F. Thomas Mitchell, M.D., Le Bonheur Children's Hospital, Memphis 5.

Additional information may be obtained from the Secretary, Council on Scientific Assembly, American Medical Association, 535 N. Dearborn St., Chicago 10.

Research Fellowships.—The National Multiple Sclerosis Society sponsors a senior postdoctoral research fellowship program intended to support the advanced, specialized training of worthy candidates interested in multiple sclerosis and the related neurological disorders.

This program is designed to be of particularly timely assistance to those candidates who have already had general postdoctoral training and who need this additional support in order to fit themselves for an academic career in this broad area of investigation.

Support is offered to candidates (1) at the senior postdoctoral level and (2) at a more advanced level where the designation of "Scholar" is given. These fellowships carry yearly stipends from $4000 to $8000 in amount, depending upon the training and experience of the candidate. A modest sum for traveling is also allowed. Ordinarily these awards are made for one year only. In exceptionally meritorious cases commitments can be made for three years.

Once an application is submitted and supported by all necessary documents the candidate can normally be notified of the decision in three weeks. For further information contact Dr. Frederick L. Stone, Director, Medical and Scientific Department, National Multiple Sclerosis Society, 270 Park Ave., New York 17.

Community Care for Handicapped Children.—Four basic guides to methods of community care for handicapped children will be issued Oct. 1 by the American Public Health Association.

The four guides have been endorsed by leading national professional organizations concerned with the health and welfare of handicapped children. They draw together significant facts and new ideas and make them available in concise form; they show how service standards have changed as research has opened new techniques and methods of prevention and treatment.

The basic guide, "Services for Handicapped Children," deals with problems common to various handicapping conditions. It outlines principles and practices to make most of existing facilities or to aid in establishing services where these are poorly organized or lacking altogether.

Three other guides which show how these general principles and practices can be used in planning services for children with such special problems are "Cerebral Palsy," "Cleft Lip and Cleft Palate," and "Dento-Facial Handicaps." These will be followed in the next two years by other guides covering such problems as diabetes, emotional disturbances, epilepsy, hearing impairment, heart disease and rheumatic fever, orthopedic and neuromuscular handicaps, and visual impairment.

The guides cover new facts about handicapped children, the causes and prevention of handicaps, finding children who need services, diagnosis and planning for care, treatment, and guidance, special services and facilities, organization of community resources, community education, personnel, research, program study, and evaluation. In addition, appendices provide such material as a check list of questions to be used in evaluating programs, check list charts of services and interagency relationships, sample procedures in a diagnostic clinic, qualifications for specialists and consultants, etc.

The Committee on Child Health of the American Public Health Association undertook this study in 1949, Dr. Samuel M. Wishik, Chairman, said, because "much of the prevailing information about the needs of children was inaccurate and often the best knowledge was unavailable to those who could use it. Significant facts needed to be drawn together, discussion provoked, opinions formulated, and agreement reached on how children may best be served through community action."

The publications are priced at $1.50 each, or at a special price of $5.10 for the set of four. Orders should be addressed to Committee on Child Health, American Public Health Association, 1790 Broadway, New York 19.

Books

The Emotional Problems of Children: A Guide for Parents. By Harry Joseph, M.D., and Gordon Zern. Price, $3.75. Pp. 310. Crown Publishers, Inc., 419 4th Ave., New York 16, 1954.

The plethora of popular publications on child guidance during the past few years makes it difficult to recommend anyone as outstanding. Dr. Harry Joseph and Gordon Zern have covered the subject in a good comprehensive manner. They are to be commended for the attention paid to "normal" developmental infant and child activities. Their explanation of abnormal behavior is clearly defined for understanding by parents.

It is interesting and instructive to find chapters related to toys, arts and crafts, and dramatics and a discussion of nursery schools.

The reviewer feels that "A Guide for Parents" is comprehensive, instructive, and tends to a practical, common-sense approach to the majority of "problems" encountered in dealing with children.

Atlas of Congenital Cardiac Disease. By Maude E. Abbott. Price, $5. Pp. 62, with 25 illustrations. American Heart Association, 50 W. 50th St., New York, 1936 (reprinted 1954).

This classic monograph, first published in 1936, has been out of print for a long time. The recent increased interest in congenital heart disease resulting from surgical achievements in this field has led to numerous requests for a reprinting.

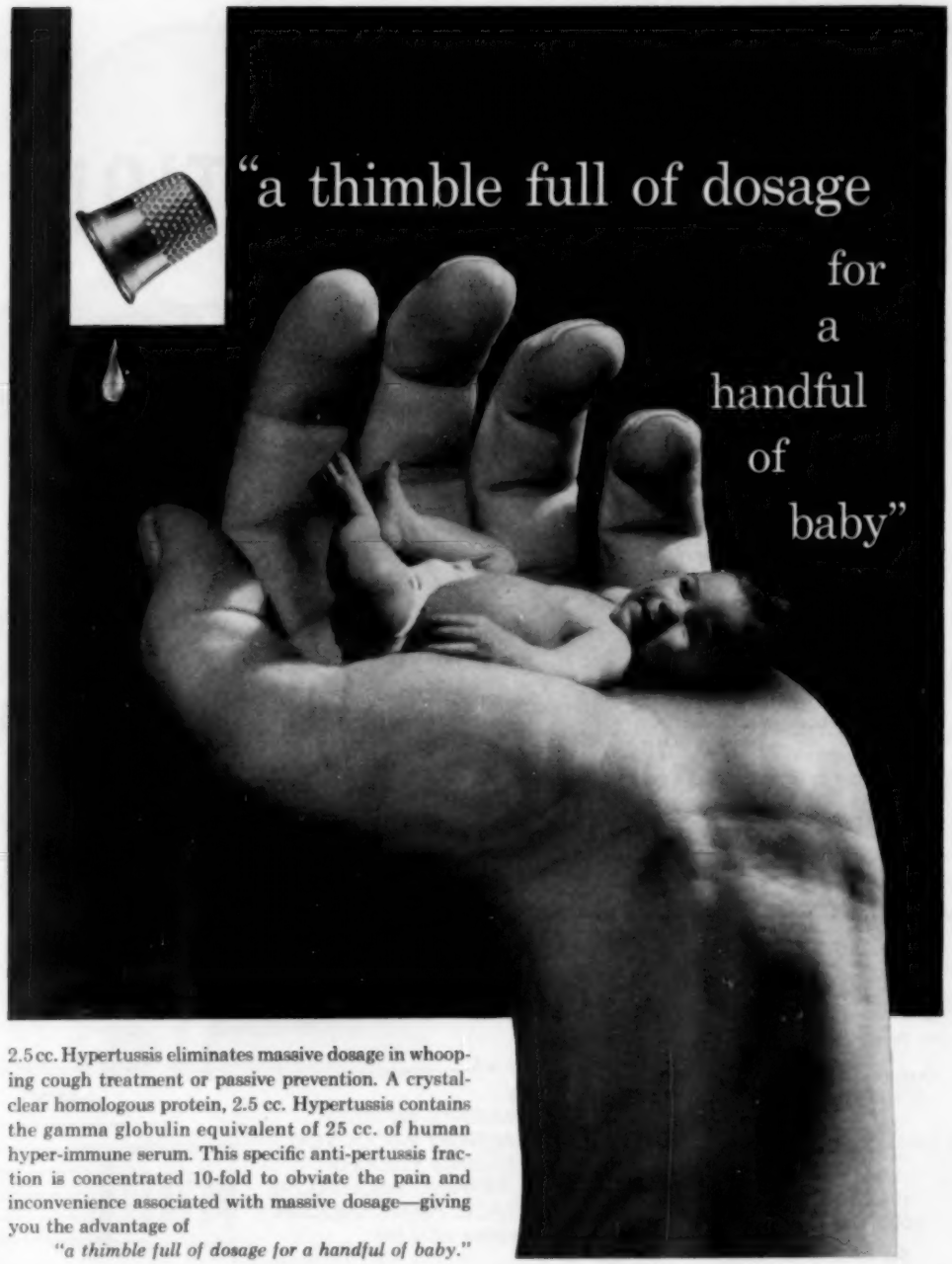
The American Heart Association has responded to these requests by printing a facsimile of the original edition in the number of 1500 copies.

The first part of the atlas is devoted to the development and comparative anatomy of the heart.

The second part classifies congenital heart lesions into three groups, depending upon the pathological physiology of the altered circulation as induced by the defect: 1. No abnormal communication (acyanotic group); 2. Arterial-venous shunt with terminal reversal of flow; 3. Venous-arterial shunt and retardation of flow.

The various lesions are discussed under these headings. Finally, there is appended a chart analyzing 1000 cases of congenital heart disease studied at autopsy.

In spite of the great advances made in our knowledge of congenital heart disease since the publication of this atlas, it should still be required reading for every serious student of this subject.



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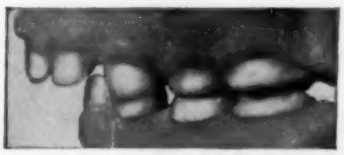

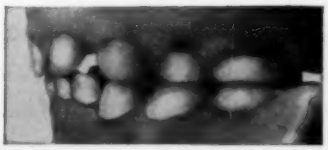

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